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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

RIGEL PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ANNORA PHARMA PRIVATE LTD., HETERO LABS LTD., and HETERO USA, INC.,** **Defendants.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Rigel Pharmaceuticals, Inc. ("Rigel"), by its undersigned attorneys, for its Complaint against Defendants Annora Pharma Private Limited ("Annora"), Hetero Labs Limited ("Hetero Labs"), and Hetero USA, Inc. ("Hetero USA") (together, "Defendants"), alleges as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. § 100, *et seq*., arising from Defendants' submission of Abbreviated New Drug Application ("ANDA") No. 217329 to the United States Food and Drug Administration ("FDA") seeking approval to manufacture, use, import, distribute, offer to sell, and/or sell generic versions of Rigel's Tavalisse® (fostamatinib disodium hexahydrate) 100 mg and 150 mg drug products

prior to the expiration of United States Patent Nos. 7,449,458 ("the '458 patent"), 8,263,122 ("the '122 patent"), 8,652,492 ("the '492 patent"), 8,771,648 ("the '648 patent"), and 8,951,504 ("the '504 patent") (collectively, "the patents-in-suit"), all owned by Rigel.

The Parties

2. Plaintiff Rigel is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1180 Veterans Boulevard, South San Francisco, CA 94080.

3. On information and belief, Defendant Annora is a corporation organized and existing under the laws of India, having a principal place of business at Sy. No. 261, Annaram Village, Gummadidala Mandal, Sangareddy Dist. Telangana State, 502313, India.

4. On information and belief, Defendant Hetero Labs is a corporation organized and existing under the laws of India, having a principal place of business at 7-2-A2, Hetero Corporate Industrial Estates, Sanath Nagar, Hyderabad 500 018, Andhra Pradesh, India.

5. On information and belief, Defendant Hetero USA is a corporation organized under the laws of Delaware, having a principal place of business at 1035 Centennial Avenue, Piscataway, NJ 08854. Upon information and belief, Hetero USA, Inc. is the U.S. Regulatory Agent for Hetero Labs and an authorized U.S. Agent for Annora, including for ANDA No. 217329.

6. On information and belief, Annora and Hetero USA are wholly-owned subsidiaries of Hetero Labs.

The Patents-in-Suit

7. On November 11, 2008, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '458 patent, entitled, "Prodrugs of 2,4-

Pyrimidinediamine Compounds and their Uses." A copy of the '458 patent is attached hereto as Exhibit A.

8. On September 11, 2012, the USPTO duly and lawfully issued the '122 patent, entitled, "Wet Granulation Using a Water Sequestering Agent." A copy of the '122 patent is attached hereto as Exhibit B.

9. On February 18, 2014, the USPTO duly and lawfully issued the '492 patent, entitled, "Wet Granulation Using a Water Sequestering Agent." A copy of the '492 patent is attached hereto as Exhibit C.

10. On July 8, 2014, the USPTO duly and lawfully issued the '648 patent, entitled, "(Trimethoxyphenylamino) Pyrimidinyl Formulations." A copy of the '648 patent is attached hereto as Exhibit D.

11. On February 10, 2015, the USPTO duly and lawfully issued the '504 patent, entitled, "(Trimethoxyphenylamino) Pyrimidinyl Formulations." A copy of the '504 patent is attached hereto as Exhibit E.

The Tavalisse® Drug Product

12. Rigel holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for fostamatinib disodium tablets (NDA No. 209299), which it sells under the trade name Tavalisse®. Tavalisse® is an FDA-approved medication used for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

13. The claims of the patents-in-suit cover, *inter alia*, fostamatinib, pharmaceutical compositions containing fostamatinib, methods of formulating fostamatinib, and methods of use and administration of pharmaceutical compositions containing fostamatinib.

14. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") with respect to Tavalisse®.

15. The labeling for Tavalisse® instructs and encourages physicians, pharmacists, and other healthcare workers and patients to administer Tavalisse® for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

16. The labeling for Tavalisse® instructs and encourages physicians, pharmacists, and other healthcare workers and patients to administer Tavalisse® according to one or more of the methods claimed in the patents-in-suit.

Acts Giving Rise To This Suit

17. On information and belief, pursuant to Section 505 of the FFDCA, Defendants submitted ANDA No. 217329 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of fostamatinib disodium 100 mg and 150 mg drug products ("Annora's Proposed Products"), before the patents-in-suit expire.

18. On information and belief, following FDA approval of ANDA No. 217329, Defendants will make, use, sell, or offer to sell Annora's Proposed Products throughout the United States, or import such generic products into the United States.

19. On information and belief, in connection with the submission of ANDA No. 217329 as described above, Defendants provided a written certification to the FDA pursuant to

Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Annora's Paragraph IV Certification"), alleging that the claims of the '458, '122, '492, '648, and '504 patents are invalid, unenforceable, and/or will not be infringed by the activities described in ANDA No. 217329.

20. No earlier than June 13, 2022, Rigel received Defendants' written notice of Annora's Paragraph IV Certification ("Annora's Notice Letter"). Annora's Notice Letter alleged that the claims of the '458, '122, '492, '648, and '504 patents are invalid and/or will not be infringed by the activities described in ANDA No. 217329. Annora's Notice Letter also informed Rigel that Defendants seek approval to market Annora's Proposed Products before the patents-in-suit expire.

Jurisdiction and Venue

21. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

22. On information and belief, Annora derives substantial revenue from directly or indirectly selling generic pharmaceutical products and/or active pharmaceutical ingredient(s) used in generic pharmaceutical products sold throughout the United States, including in this Judicial District.

23. This Court has personal jurisdiction over Annora because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in the State of New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Hetero USA, a company with a regular and established place of business in New Jersey; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing,

distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Hetero Labs and Hetero USA.

24. On information and belief, Hetero Labs derives substantial revenue from directly or indirectly selling generic pharmaceutical products and/or active pharmaceutical ingredient(s) used in generic pharmaceutical products sold throughout the United States, including in this Judicial District.

25. This Court has personal jurisdiction over Hetero Labs because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in the State of New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Hetero USA, a company with a regular and established place of business in New Jersey; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Annora and Hetero USA.

26. On information and belief, Hetero USA derives substantial revenue from directly or indirectly selling generic pharmaceutical products and/or active pharmaceutical ingredient(s) used in generic pharmaceutical products sold throughout the United States, including in this Judicial District.

27. This Court has personal jurisdiction over Hetero USA because, *inter alia*, it: (1) on information and belief, maintains a regular and established, physical place of business at 1035 Centennial Avenue, Piscataway, NJ 08854; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Annora. By virtue of its physical presence in New Jersey, this Court has personal jurisdiction over Hetero

USA. On information and belief, Hetero USA purposefully has conducted and continues to conduct business in this Judicial District.

28. On information and belief, Annora, Hetero Labs, and Hetero USA are in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. On information and belief, Annora, Hetero Labs, and Hetero USA also prepare and/or aid in the preparation and submission of ANDAs to the FDA, including ANDA No. 217329.

29. On information and belief, this Judicial District is a likely destination for the generic drug products described in ANDA No. 217329.

30. On information and belief, Annora, Hetero Labs, and Hetero USA derive substantial revenue from directly or indirectly selling generic pharmaceutical products and/or active pharmaceutical ingredient(s) used in generic pharmaceutical products sold throughout the United States, including in this Judicial District.

31. This Court also has personal jurisdiction over Annora, Hetero Labs, and Hetero USA because, *inter alia*, they have committed an act of patent infringement under 35 U.S.C. § 271(e)(2). On information and belief, Annora, Hetero Labs, and Hetero USA intend a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to Rigel in New Jersey and in this Judicial District.

32. In the alternative, this Court has personal jurisdiction over Annora because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Rigel's claims arise under federal law; (b) Annora is a foreign defendant not subject to general personal jurisdiction in the

courts of any state; and (c) Annora has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Annora satisfies due process.

33. In the alternative, this Court has personal jurisdiction over Hetero Labs because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Rigel's claims arise under federal law; (b) Hetero Labs is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Hetero Labs has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Hetero Labs satisfies due process.

34. On information and belief, Annora, Hetero Labs, and Hetero USA work in privity and/or concert either directly or indirectly through one or more of their wholly owned subsidiaries with respect to the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products throughout the United States, including in this Judicial District.

35. On information and belief, each of Annora, Hetero Labs, and Hetero USA actively participated in the submission of ANDA No. 217329. On information and belief, Annora, Hetero Labs, and Hetero USA will work in privity and/or concert with one another and/or other related entities towards the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including

Annora's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the patents-in-suit.

36. On information and belief, Annora intends to benefit directly if ANDA No. 217329 is approved by participating in the manufacture, importation, distribution, and/or sale of the generic drug products that are the subject of ANDA No. 217329.

37. On information and belief, Hetero Labs intends to benefit directly if ANDA No. 217329 is approved by participating in the manufacture, importation, distribution, and/or sale of the generic drug products that are the subject of ANDA No. 217329.

38. On information and belief, Hetero USA intends to benefit directly if ANDA No. 217329 is approved by participating in the manufacture, importation, distribution, and/or sale of the generic drug products that are the subject of ANDA No. 217329.

39. On information and belief, Annora and Hetero USA act at the direction, and for the benefit, of Hetero Labs and are controlled and/or dominated by Hetero Labs.

40. On information and belief, Annora, Hetero Labs, and Hetero USA act, operate, and/or hold themselves out to the public as a single integrated business.

41. On information and belief, Annora, Hetero Labs, and Hetero USA have previously been sued in this District and have not challenged personal jurisdiction. *See, e.g., Celgene Corporation v. Annora Pharma Private Limited, et al.*, C.A. No. 3-18-cv-11220 (D.N.J. June 28, 2018) (Annora, Hetero USA); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 19-15449 (SDW)(LDW) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 19-5797 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 18-17463 (SDW)(LDW) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs*

Limited, et al., Civil Action No. 18-14111 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 17-3387 (ES)(MAH) (D.N.J.) (Hetero USA, Hetero Labs); *Otsuka Pharm. Co., Ltd. v. Hetero Drugs Ltd., et al.*, Civil Action No. 15-161 (JBS)(KMW) (D.N.J.) (Hetero USA, Hetero Labs); *AstraZeneca AB, et al. v. Hetero USA Inc., et al.*, Civil Action No. 16-2442 (RMB)(JS) (D.N.J.) (Hetero USA and Hetero Labs); and *BTG Int'l Ltd., et al. v. Actavis Labs. FL, Inc., et al.*, Civil Action No. 15-5909 (KM)(JBC) (D.N.J.) (Hetero USA, Hetero Labs).

42. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

Count I: Infringement of the '458 Patent

43. Rigel repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

44. Defendants' submission of ANDA No. 217329, with the accompanying Paragraph IV Certification and notice to Rigel of same, to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Annora's Proposed Products, prior to the expiration of the '458 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

45. There is a justiciable controversy between the parties hereto as to the infringement of the '458 patent.

46. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will infringe one or more claims of the '458 patent, including at least claim 1, under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States.

47. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will induce infringement of one or more claims of the '458 patent, including at least claim 1, under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, upon FDA approval of ANDA No. 217329, Defendants will intentionally encourage acts of direct infringement with knowledge of the '458 patent and knowledge that their acts are encouraging infringement.

48. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will contributorily infringe one or more claims of the '458 patent, including at least claim 1, under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, Defendants have had and continue to have knowledge that Annora's Proposed Products are especially adapted for a use that infringes one or more claims of the '458 patent and that there is no substantial non-infringing use for Annora's Proposed Products.

49. Rigel will be substantially and irreparably damaged and harmed if Defendants' infringement of the '458 patent is not enjoined.

50. Rigel does not have an adequate remedy at law.

51. This case is an exceptional one, and Rigel is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '122 Patent

52. Rigel repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

53. Defendants' submission of ANDA No. 217329, with the accompanying Paragraph IV Certification and notice to Rigel of same, to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Annora's Proposed Products, prior to the expiration of the '122 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

54. There is a justiciable controversy between the parties hereto as to the infringement of the '122 patent.

55. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will infringe one or more claims of the '122 patent, including at least claim 1, under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States.

56. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will induce infringement of one or more claims of the '122 patent, including at least claim 1, under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, upon FDA approval of ANDA No. 217329, Defendants will intentionally encourage acts of direct infringement with knowledge of the '122 patent and knowledge that their acts are encouraging infringement.

57. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will contributorily infringe one or more claims of the '122 patent, including at least claim 1, under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, Defendants have had and continue to have knowledge that Annora's Proposed Products are especially adapted for

a use that infringes one or more claims of the '122 patent and that there is no substantial non-infringing use for Annora's Proposed Products.

58. Rigel will be substantially and irreparably damaged and harmed if Defendants' infringement of the '122 patent is not enjoined.

59. Rigel does not have an adequate remedy at law.

60. This case is an exceptional one, and Rigel is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '492 Patent

61. Rigel repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

62. Defendants' submission of its ANDA, with the accompanying Paragraph IV Certification and notice to Rigel of same, to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Annora's Proposed Products, prior to the expiration of the '492 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

63. There is a justiciable controversy between the parties hereto as to the infringement of the '492 patent.

64. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will infringe one or more claims of the '492 patent, including at least claim 1, under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States.

65. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will induce infringement of one or more claims of the '492 patent, including at least

claim 1, under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, upon FDA approval of ANDA No. 217329, Defendants will intentionally encourage acts of direct infringement with knowledge of the '492 patent and knowledge that their acts are encouraging infringement.

66. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will contributorily infringe one or more claims of the '492 patent, including at least claim 1, under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, Defendants have had and continue to have knowledge that Annora's Proposed Products are especially adapted for a use that infringes one or more claims of the '492 patent and that there is no substantial non-infringing use for Annora's Proposed Products.

67. Rigel will be substantially and irreparably damaged and harmed if Defendants' infringement of the '492 patent is not enjoined.

68. Rigel does not have an adequate remedy at law.

69. This case is an exceptional one, and Rigel is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '648 Patent

70. Rigel repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

71. Defendants' submission of ANDA No. 217329, with the accompanying Paragraph IV Certification and notice to Rigel of same, to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Annora's Proposed Products, prior to the

expiration of the '648 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

72. There is a justiciable controversy between the parties hereto as to the infringement of the '648 patent.

73. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will infringe one or more claims of the '648 patent, including at least claim 1, under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States.

74. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will induce infringement of one or more claims of the '648 patent, including at least claim 1, under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, upon FDA approval of ANDA No. 217329, Defendants will intentionally encourage acts of direct infringement with knowledge of the '648 patent and knowledge that their acts are encouraging infringement.

75. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will contributorily infringe one or more claims of the '648 patent, including at least claim 1, under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, Defendants have had and continue to have knowledge that Annora's Proposed Products are especially adapted for a use that infringes one or more claims of the '648 patent and that there is no substantial non-infringing use for Annora's Proposed Products.

76. Rigel will be substantially and irreparably damaged and harmed if Defendants' infringement of the '648 patent is not enjoined.

77. Rigel does not have an adequate remedy at law.

78. This case is an exceptional one, and Rigel is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '504 Patent

79. Rigel repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

80. Defendants' submission of ANDA No. 217329, with the accompanying Paragraph IV Certification and notice to Rigel of same, to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Annora's Proposed Products, prior to the expiration of the '504 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

81. There is a justiciable controversy between the parties hereto as to the infringement of the '504 patent.

82. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will infringe one or more claims of the '504 patent, including at least claim 22, under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States.

83. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will induce infringement of one or more claims of the '504 patent, including at least claim 22, under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, upon FDA

approval of ANDA No. 217329, Defendants will intentionally encourage acts of direct infringement with knowledge of the '504 patent and knowledge that their acts are encouraging infringement.

84. Unless enjoined by this Court, upon FDA approval of ANDA No. 217329, Defendants will contributorily infringe one or more claims of the '504 patent, including at least claim 22, under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Annora's Proposed Products in the United States. On information and belief, Defendants have had and continue to have knowledge that Annora's Proposed Products are especially adapted for a use that infringes one or more claims of the '504 patent and that there is no substantial non-infringing use for Annora's Proposed Products.

85. Rigel will be substantially and irreparably damaged and harmed if Defendants' infringement of the '504 patent is not enjoined.

86. Rigel does not have an adequate remedy at law.

87. This case is an exceptional one, and Rigel is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Rigel respectfully requests the following relief:

(A) A Judgment that Defendants have infringed the patents-in-suit by submitting ANDA No. 217329 with the accompanying Paragraph IV Certification and notice to Rigel of same;

(B) A Judgment that Defendants have infringed, and that Annora's making, using, selling, offering to sell, or importing Annora's Proposed Products will infringe, one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 217329 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Rigel is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Defendants and their officers, agents, attorneys, and employees, and those acting in privity and/or concert with them, from making, using, offering to sell, selling, or importing Annora's Proposed Products until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Rigel is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Annora, its officers, agents, attorneys and employees, and those acting in privity and/or concert with it, from practicing any pharmaceutical compositions containing fostamatinib, as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Rigel is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Annora's Proposed Products will directly infringe, and induce and/or contribute to infringement of, the patents-in-suit;

(G) To the extent that Defendants, their officers, agents, attorneys, and/or employees, or those acting in privity and/or concert with them, have committed any acts with respect to the pharmaceutical compositions containing fostamatinib claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Rigel damages for such acts;

(H) If Defendants, their officers, agents, attorneys, and/or employees, or those acting in privity and/or concert with them, engages in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Annora's Proposed Products prior to the expiration of the patents-in-suit, a Judgment awarding damages to Rigel resulting from such infringement, together with interest;

(I) A Judgment declaring that the patents-in-suit remain valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Rigel its attorneys' fees incurred in this action;

(K) A Judgment awarding Rigel its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: July 25, 2022

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: July 25, 2022

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EXHIBIT A

US007449458B2

(12) **United States Patent**
Bhamidipati et al.

(10) **Patent No.: US 7,449,458 B2**
(45) **Date of Patent: Nov. 11, 2008**

(54) **PRODRUGS OF 2,4-PYRIMIDINEDIAMINE COMPOUNDS AND THEIR USES**

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See application file for complete search history.

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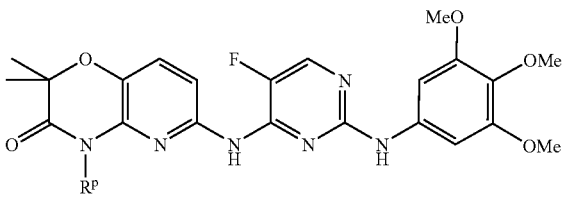
(57) **ABSTRACT**

The present disclosure provides prodrugs of biologically active 2,4-pyrimidinediamine compounds of structural formula shown below, compositions comprising these compounds, intermediates and methods for synthesizing these compounds, and methods for using these compounds in a variety of applications including treatment of autoimmune diseases.



13 Claims, 12 Drawing Sheets

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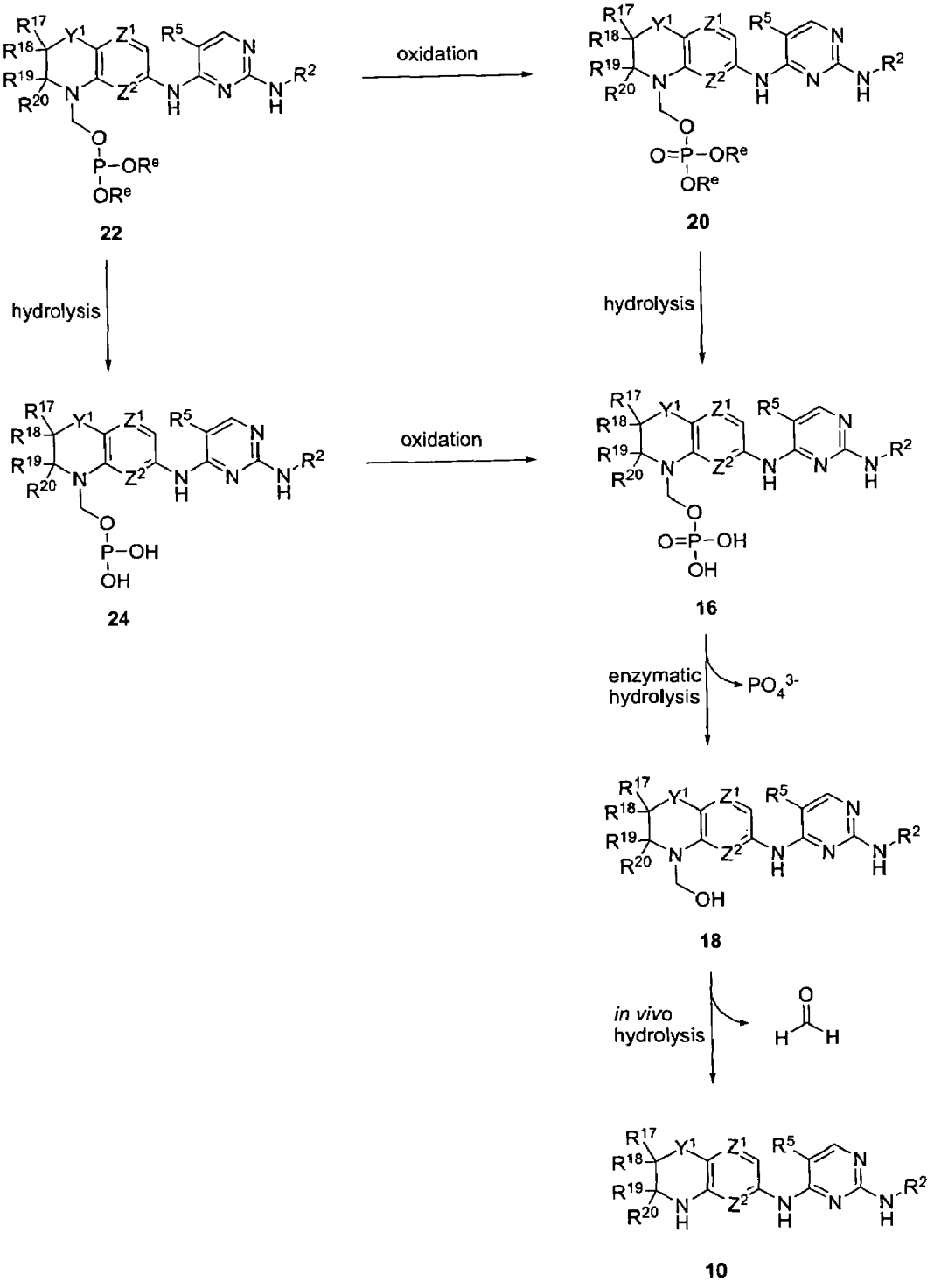
FIG. 1A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20
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16
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18
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10

FIG. 1B

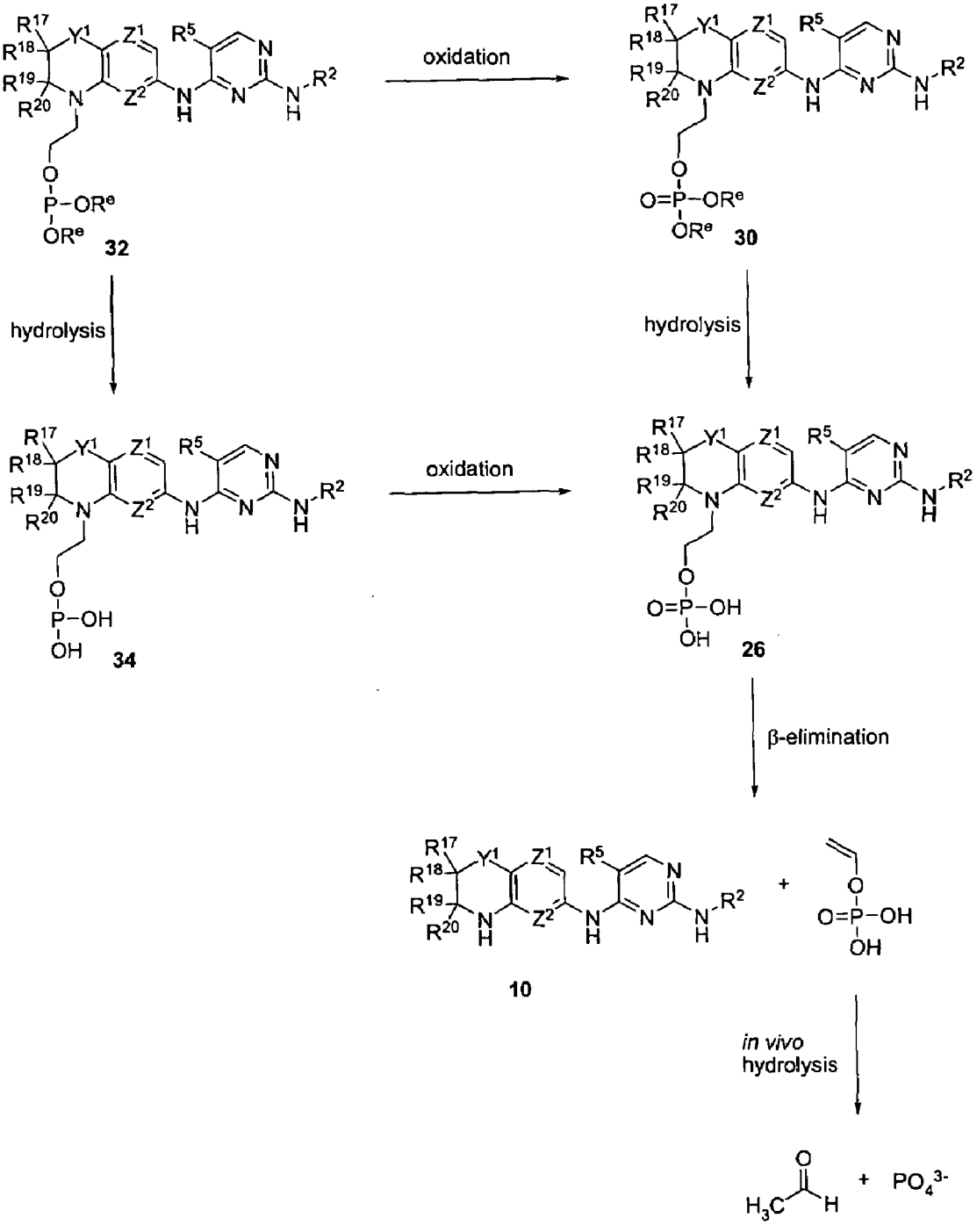

oxidation
hydrolysis
hydrolysis
oxidation
β-elimination
in vivo
hydrolysis
32
30
34
26
10
+
+ PO4 3-

FIG. 2

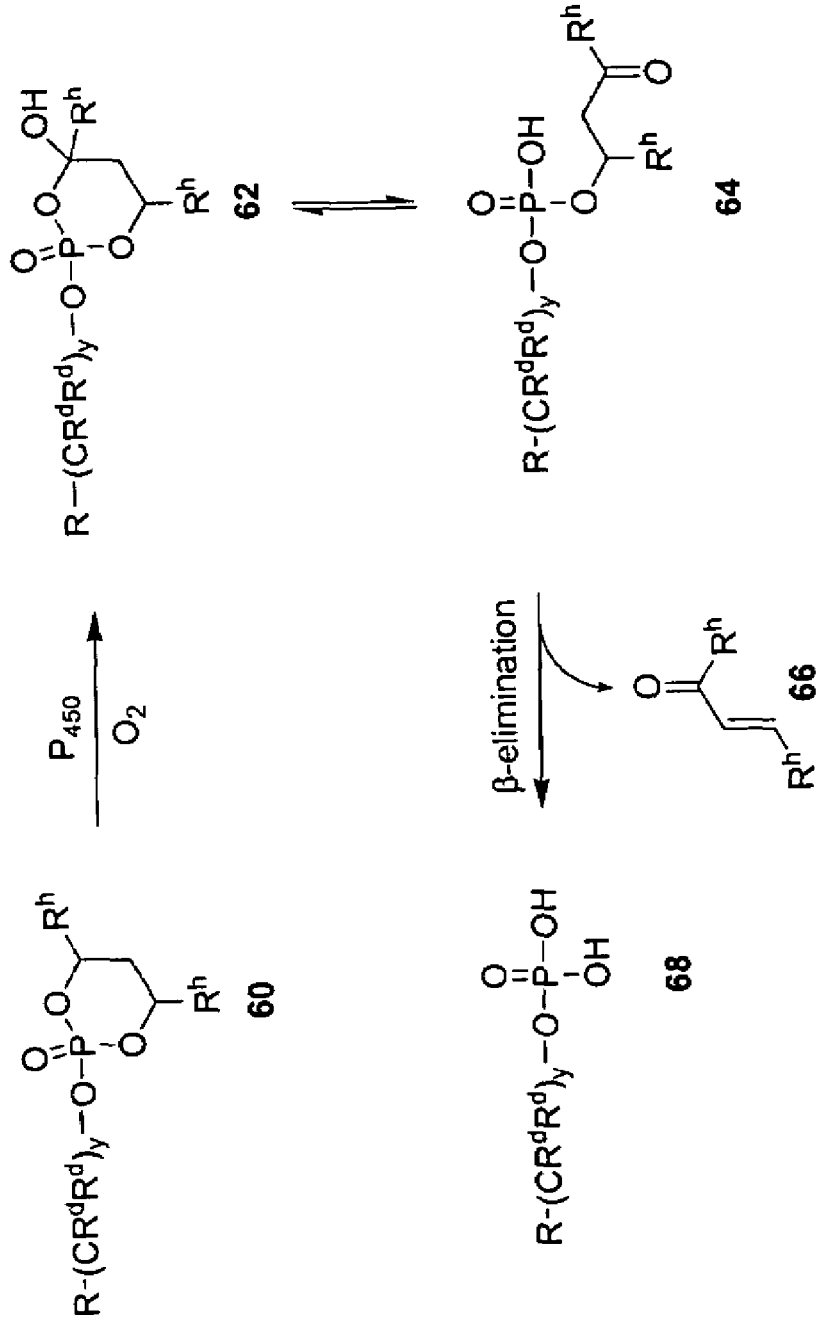


FIG. 3

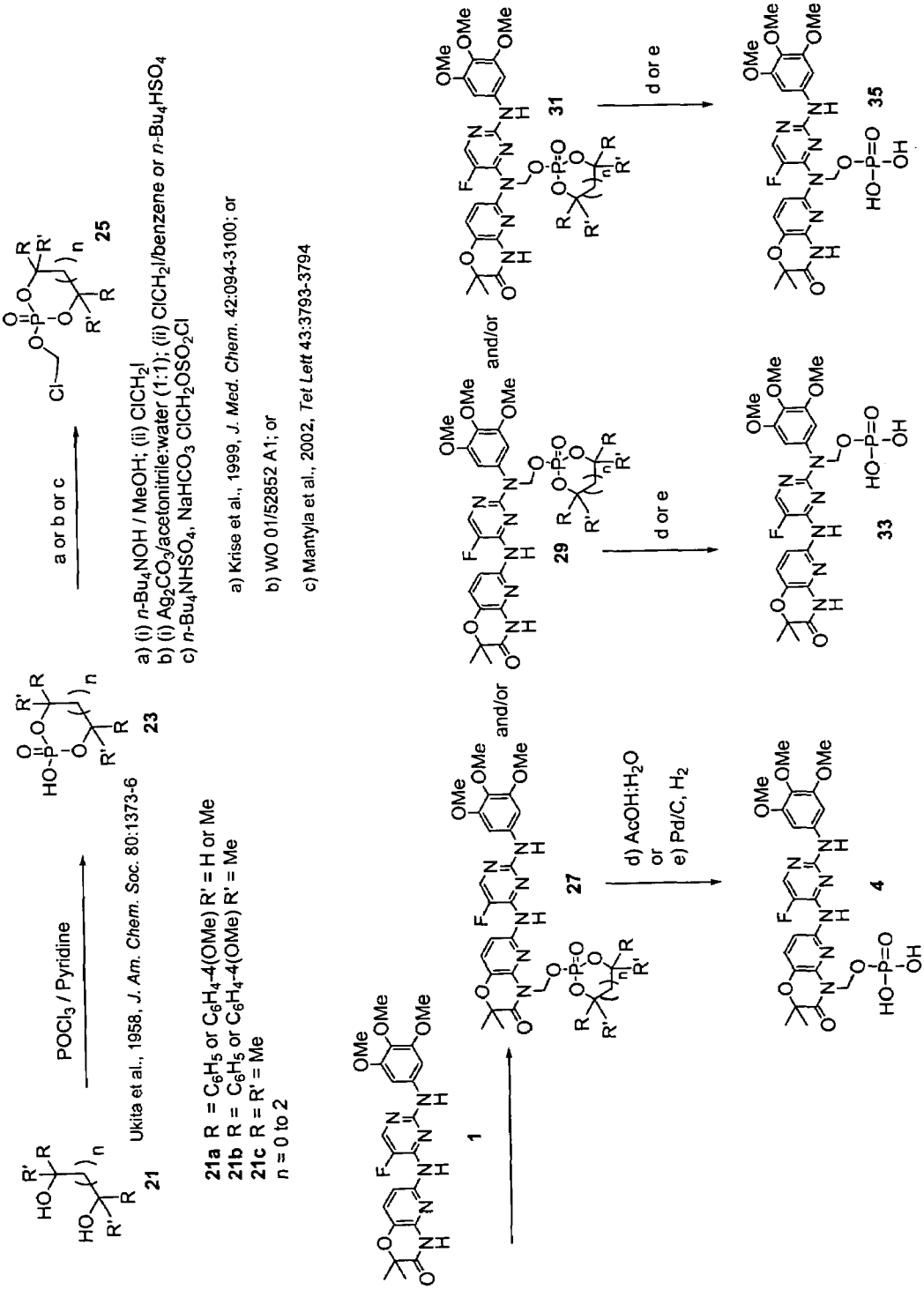
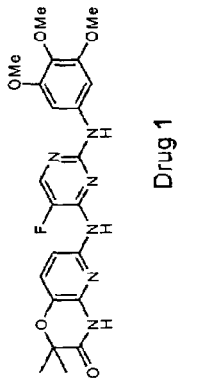
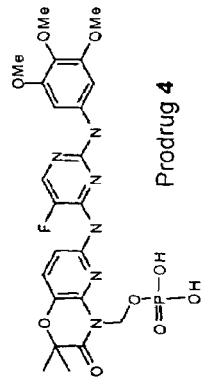

POCl3 / Pyridine
Ukita et al., 1958, J. Am. Chem. Soc. 80:1373-6
21a R = C6H5 or C6H4-4(OMe) R' = H or Me
21b R = C6H5 or C6H4-4(OMe) R' = Me
21c R = R' = Me
n = 0 to 2
21
23
25
a or b or c
a) (i) n-Bu4NOH / MeOH; (ii) ClCH2I
b) (i) Ag2CO3/acetonitrile:water (1:1); (ii) ClCH2I/benzene or n-Bu4HSO4
c) n-Bu4NHSO4, NaHCO3 ClCH2OSO2Cl
a) Krise et al., 1999, J. Med. Chem. 42:094-3100; or
b) WO 01/52852 A1; or
c) Mantyla et al., 2002, Tet Lett 43:3793-3794
1
27
29
31
33
35
4
and/or
d or e
d) AcOH:H2O
or
e) Pd/C, H2

FIG. 4

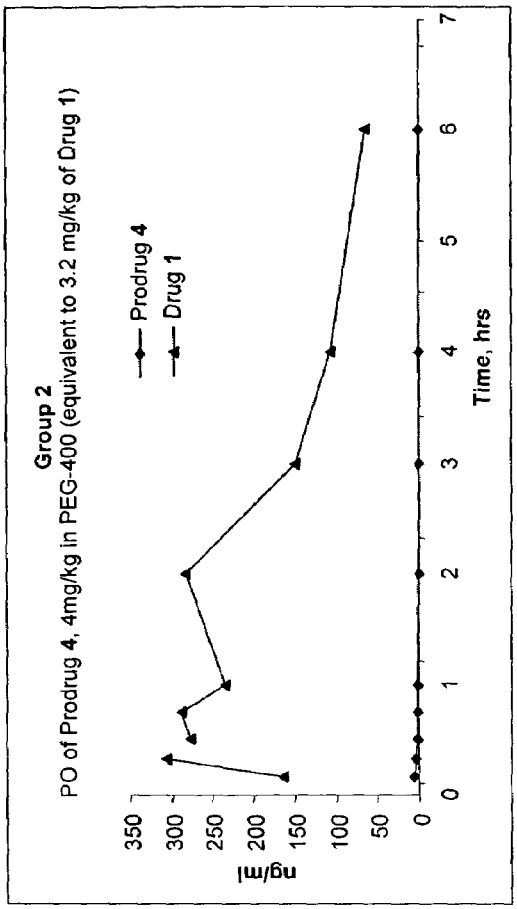
Rat PK Profiles for Prodrug Compound **4**



Drug 1



Prodrug **4**



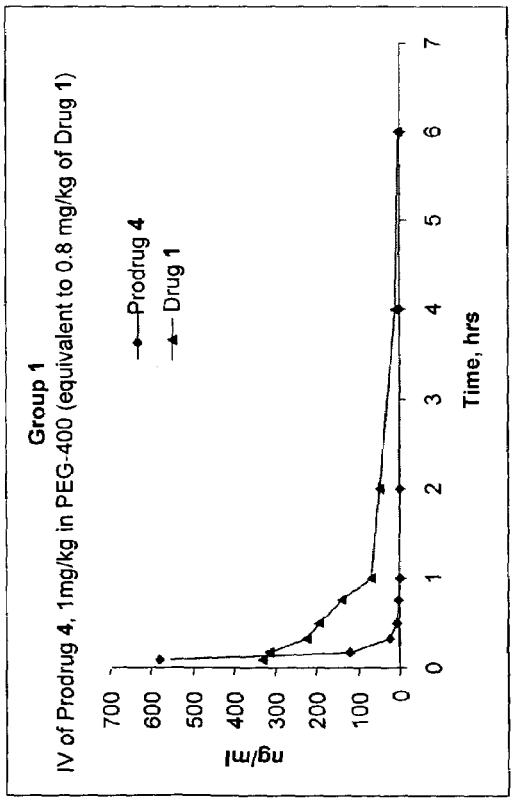


FIG. 5

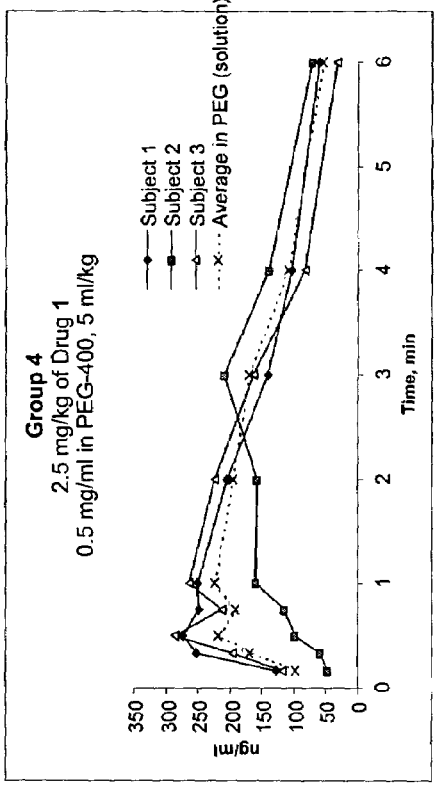
PK Summary

Mode of Delivery	Analyte	Parameter	Value	Comments
IV	Prodrug **4**	Clearance, ml/min/kg	93.1	AUC of **4** = 182 AUC of **1** = 327
		T1/2, hr	0.2	
PO	Drug **1**	%F	29.9	Total absorbed and converted to Drug **1**
		Cmax, ng/ml	331	
	Prodrug **4**	%F	0.3	
		Cmax, ng/ml	5.23	

FIG. 6

Comparison of Drug Exposure – Prodrug **4** vs Drug **1** in PEG-400

Compound	Dose (Drug 1 mg/kg)	AUC/dose
Drug 1	2.5	345
Prodrug 4	3.2	316



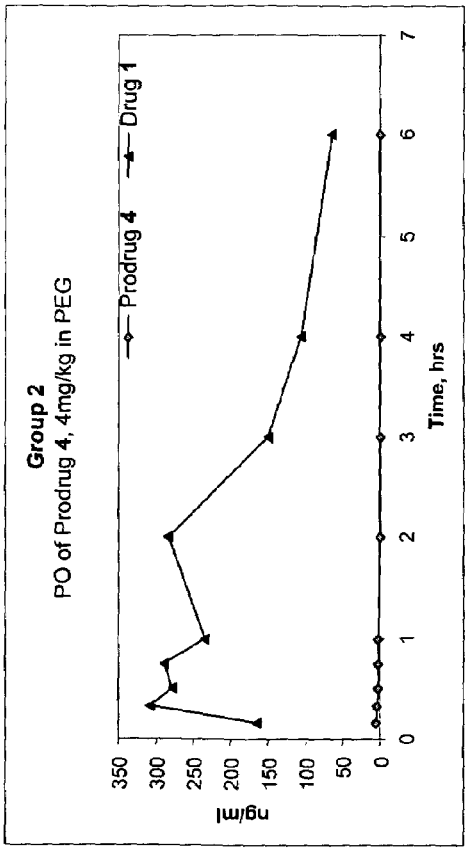
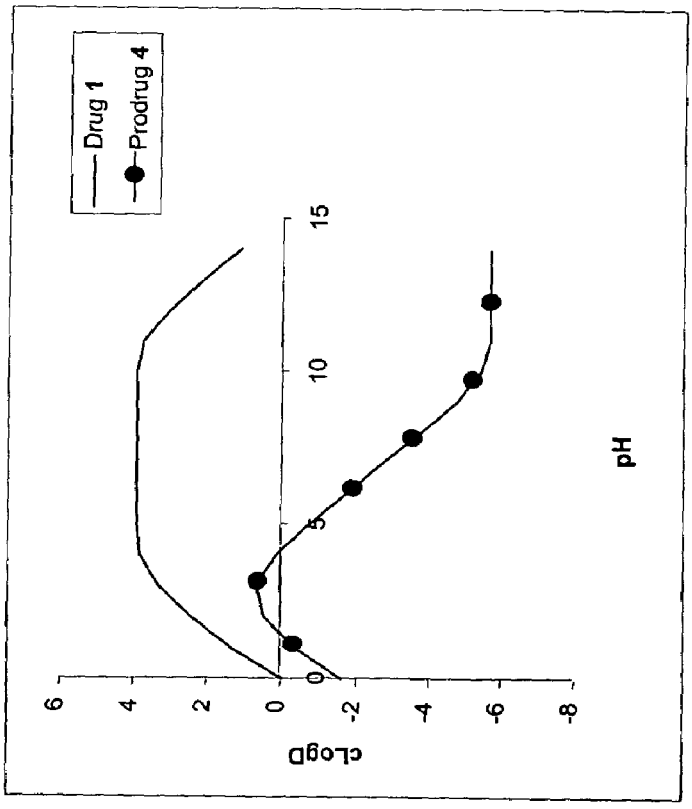


FIG. 7

cLogD vs pH (Pallas) and Measured Solubility



- Solubility (Prodrug 4) in Phosphate buffer (pH = 7.5, 100 mM)
- Conditions:
  - 0.4mg in 80 ul buffer (5 mg/ml). Insoluble material removed by centrifugation at 2 and 24hrs.
  - LC/MS/MS analysis.

Time, hrs	Solubility, mg/ml replicate 1	replicate 2
2	5.04	4.94
24	5.09	5.03

FIG. 8

Chemical Stability of Prodrug **4**

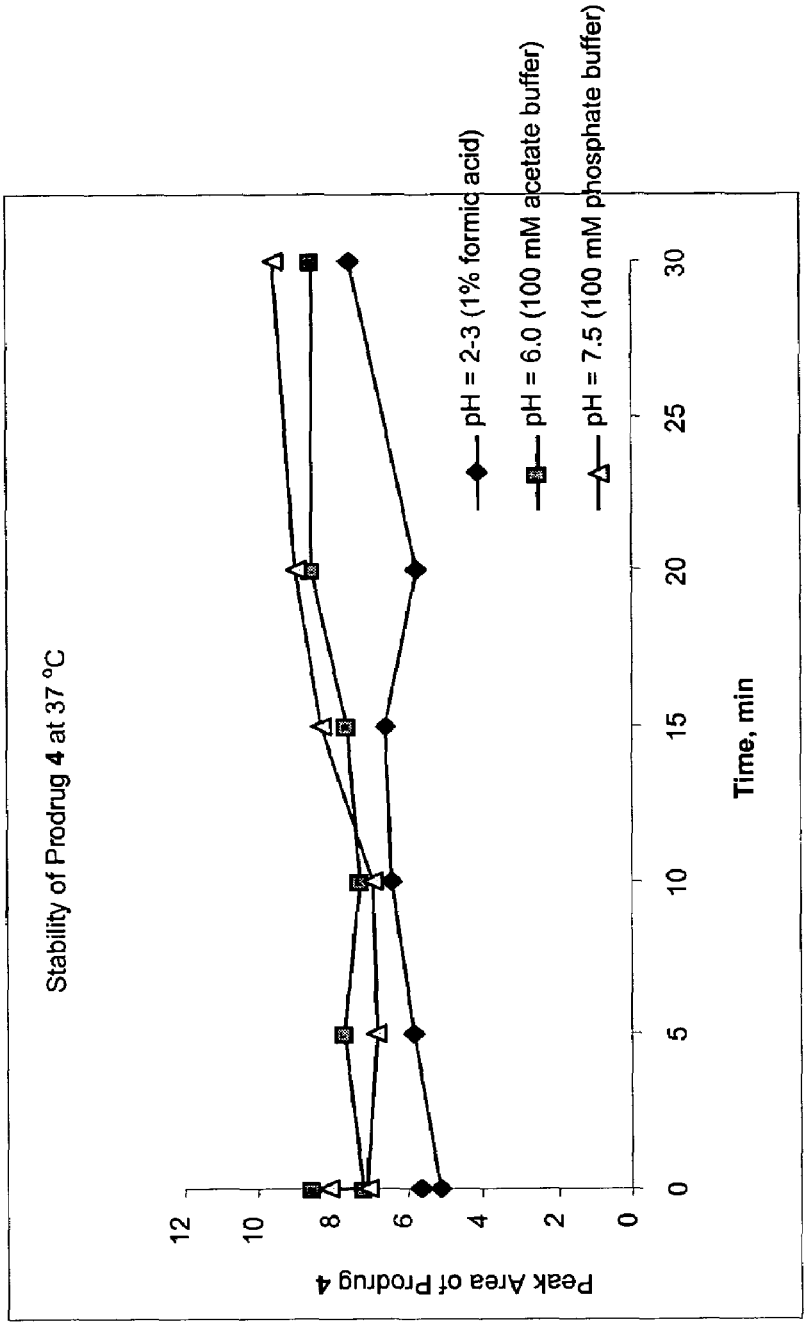
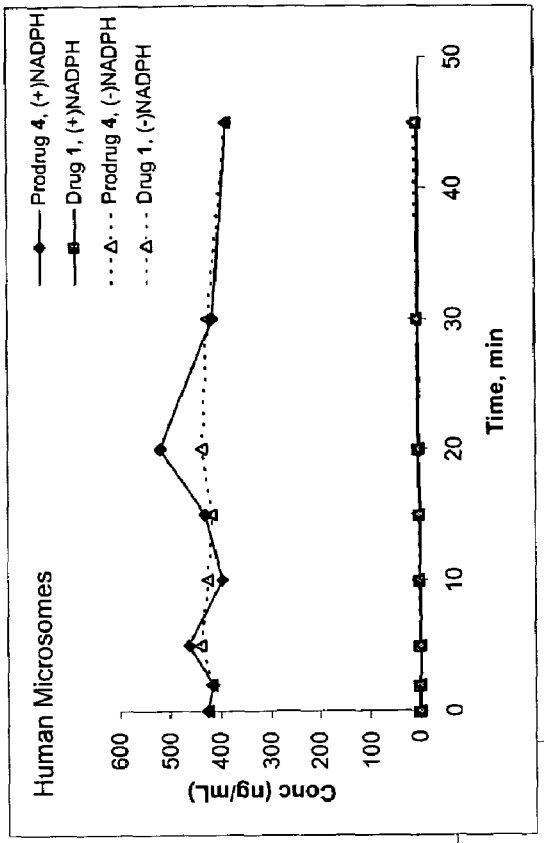


FIG. 9

Metabolic Stability: Microsomes

- p-nitrophenyl phosphate (PNP) is stable in microsomes and S9 fractions.
- PNP is a known substrate for both acid and alkaline phosphatase



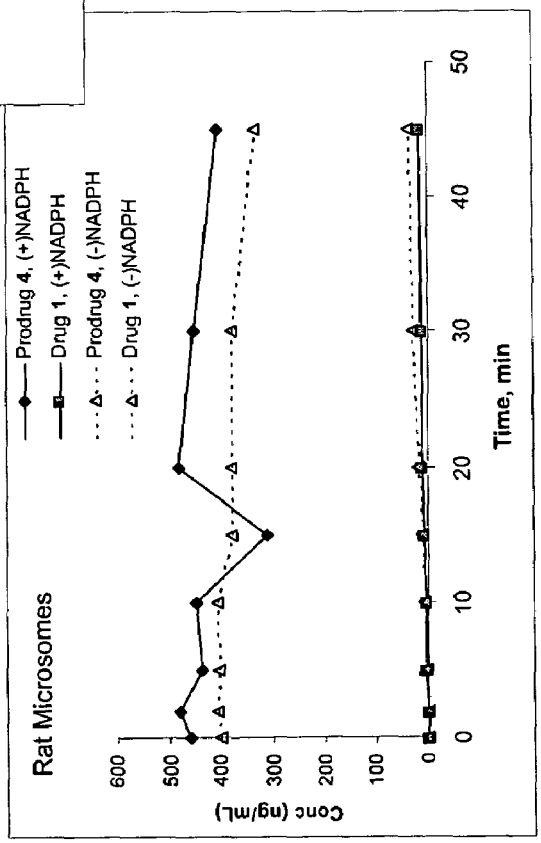
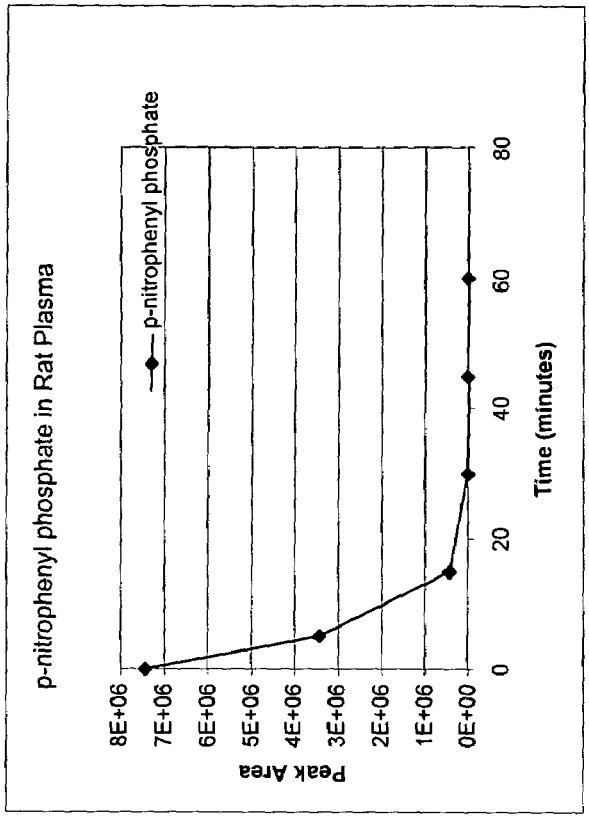


FIG. 10

Plasma Stability (Rat) of Prodrug **4** and PNP



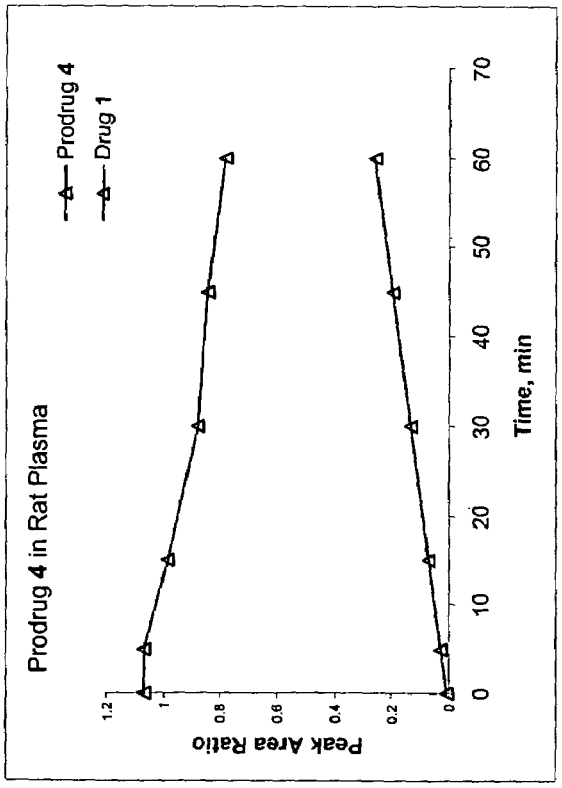
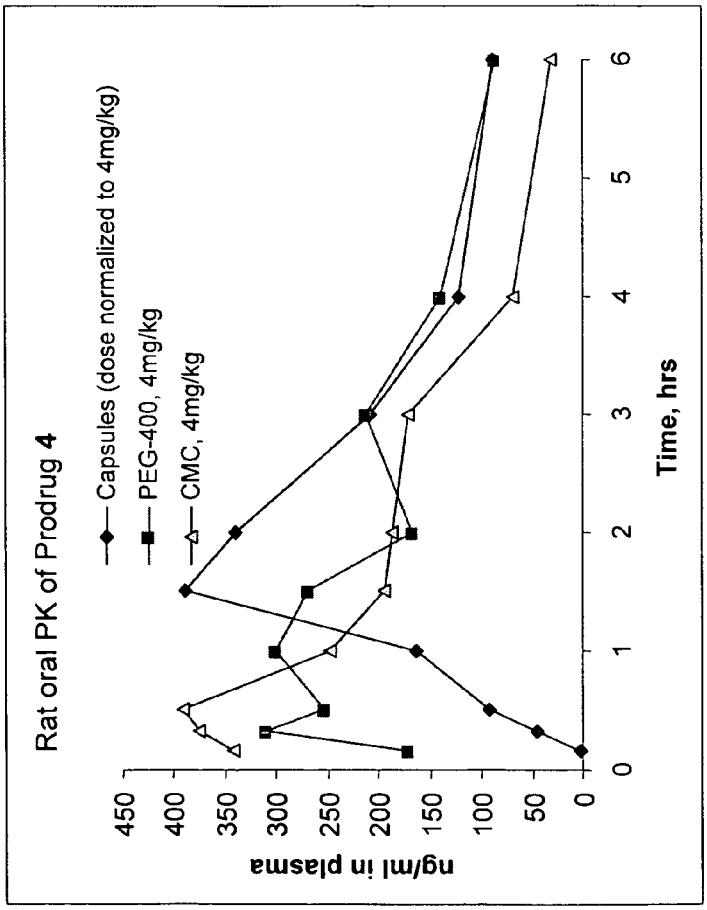


FIG. 11

Rat PK Study of Prodrug **4**

– Oral Delivery:
  - Solutions: Carboxymethylcellulose (CMC) and PEG (0.8 mg/ml Prodrug **4**), 5ml/kg
  - Powder: #9 Hard gelatin capsules (HGC), 5.7 – 6.9 mg Prodrug **4** /capsule

Vehicle	AUC	SD
PEG-400	914	79
CMC	1083	78.2
HGC	1049	292



PRODRUGS OF 2,4-PYRIMIDINEDIAMINE COMPOUNDS AND THEIR USES

1. CROSS-REFERENCE

This application claims benefit under 35 U.S.C. §119(e) to provisional application Ser. No. 60/645,424, filed Jan. 19, 2005 and provisional application Ser. No. 60/654,620, filed Feb. 18, 2005. The disclosures of both of these provisional applications are incorporated herein by reference in their entireties.

2. FIELD

The present disclosure relates to prodrugs of biologically active 2,4-pyrimidinediamine compounds, pharmaceutical compositions comprising the prodrugs, intermediates and synthetic methods of making the prodrugs and methods of using the prodrugs and compositions in a variety of contexts, such as in the treatment or prevention of various diseases.

3. BACKGROUND

Crosslinking of Fc receptors, such as the high affinity receptor for IgE (FcεRI) and/or the high affinity receptor for IgG (FcγRI) activates a signaling cascade in mast, basophil and other immune cells that results in the release of chemical mediators responsible for numerous adverse events. For example, such crosslinking leads to the release of preformed mediators of Type I (immediate) anaphylactic hypersensitivity reactions, such as histamine, from storage sites in granules via degranulation. It also leads to the synthesis and release of other mediators, including leukotrienes, prostaglandins and platelet-activating factors (PAFs), that play important roles in inflammatory reactions. Additional mediators that are synthesized and released upon crosslinking Fc receptors include cytokines and nitric oxide.

The signaling cascade(s) activated by crosslinking Fc receptors such as FcεRI and/or FcγRI comprises an array of cellular proteins. Among the most important intracellular signal propagators are the tyrosine kinases. And, an important tyrosine kinase involved in the signal transduction pathways associated with crosslinking the FcεRI and/or FcγRI receptors, as well as other signal transduction cascades, is Syk kinase (see Valent et al., 2002, Intl. J. Hematol. 75(4):257-362 for review).

The mediators released as a result of FcεRI and FcγRI receptor cross-linking are responsible for, or play important roles in, the manifestation of numerous adverse events. Recently, various-classes of 2,4-pyrimidinediamine compounds have been discovered that inhibit the FcεRI and/or FcγRI signaling cascades, and that have myriad therapeutic uses. See, e.g., U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US 2004/0029902A1), international application Ser. No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO 2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893). While many of these compounds exhibit good bioavailability properties, in some instances it may be desirable to tailor their solubility or other properties such that their bioavailability via specified routes of administration is optimized.

4. SUMMARY

The present disclosure provides prodrugs of 2,4-pyrimidinediamine compounds that have myriad biological activities, and hence therapeutic uses, compositions comprising the prodrugs, methods and intermediates useful for synthesizing the prodrugs and methods of using the prodrugs in a variety of in vitro and in vivo contexts, including in the treatment and/or prevention of diseases mediated, at least in part, by the activation of Fc receptor signaling cascades.

The prodrugs generally comprise a biologically active 2,4-pyrimidinediamine compound that is substituted at the nitrogen atom of one or more primary or secondary amine groups with a progroup R^P that metabolizes or otherwise transforms under conditions of use to yield the active 2,4-pyrimidinediamine. In some embodiments, the progroup R^P is a phosphorous-containing progroup. In some embodiments, the progroup includes a group or moiety that is metabolized under the conditions of use to yield an unstable α-hydroxymethyl, α-aminomethyl or α-thiomethyl intermediate, which then further metabolized in vivo to yield the active 2,4-pyrimidinediamine drug. In some embodiments, the progroup includes an α-hydroxyalkyl, α-aminoalkyl or α-thioalkyl moiety, for example an α-hydroxymethyl, α-aminomethyl, α-thiomethyl moiety, that metabolizes under the conditions of use to yield the active 2,4 pyrimidinediamine drug. For example, in some embodiments the progroup R^P is of the formula —CR^dR^d-AR^3, where each R^d is, independently of the other, selected from hydrogen, cyano, optionally substituted (C1-C20) alkyl, (C1-C20) perfluoroalkyl, optionally substituted (C7-C30) arylalkyl and optionally substituted 6-30 membered heteroarylalkyl, where each optional substituent is, independently of the others, selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl and heteroalkyl, or, alternatively, the two R^d are taken together with the carbon atom to which they are bonded to form a cycloalkyl containing from 3 to 8 carbon atoms ; A is selected from O, S and NR^{50}, where R^{50} is selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and cycloheteroalkyl, or alternatively is combined with R^3, and, together with the nitrogen to which they are attached, form a three to seven membered ring; and R^3 represents a group that can be metabolized in vivo to yield a group of the formula —CR^dR^d-AH, where R^d and A are as previously defined.

The identity of R^3 is not critical, provided that it can be metabolized under the desired conditions of use, for example under the acidic conditions found in the stomach and/or by enzymes found in vivo, to yield a group of the formula —CR^dR^d-AH, where A and R^d are as previously defined. Thus, skilled artisans will appreciate that R^3 can comprise virtually any known or later-discovered hydroxyl, amine or thiol protecting group. Non-limiting examples of suitable protecting groups can be found, for example, in *Protective Groups in Organic Synthesis*, Greene & Wuts, 2nd Ed., John Wiley & Sons, New York, 1991 (especially pages 10-142 (alcohols, 277-308 (thiols) and 309-405 (amines) the disclosure of which is incorporated herein by reference).

In a specific embodiment, R^3 includes, together with A, an ether, a thioether, a silyl ether, a silyl thioether, an ester, a thioester, an amide, a carbonate, a thiocarbonate, a carbamate, a thiocarbamate, or a urea linkage, —OCH_2SO_3R, where R is hydrogen, alkyl, aryl, arylalkyl or a metal salt (e.g., sodium, lithium, potassium); -$GCH_2{}^+N(R^{51})_3M^-$, where G is absent, —OPO_3—, OSO_3— or —CO_2—, R^{51} is hydrogen, alkyl, aryl, arylalkyl, cycloheteroalkyl or cycloheteroalkylalkyl and M− is a counterion, usually a halide ion or the like (acetate, sulfate, phosphate, etc.). Specific exemplary

embodiments include, but are not limited to, progroups R^P in which R^3 is selected from R^f, —C(O)R^f, —C(O)OR^f, —C(O)NR^fR^f and —Si$R^fR^fR^f$, where each R^f is, independently of the others, selected from hydrogen, optionally substituted lower alkyl, optionally substituted lower heteroalkyl, optionally substituted lower cycloalkyl, optionally substituted lower heterocycloalkyl, optionally substituted (C6-C10) aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted (C7-C18) arylalkyl and optionally substituted 6-18 membered heteroarylalkyl. In a specific embodiment, each R^f is the same.

The identity of the progroup(s) R^p can be selected to tailor the water-solubility and other properties of the underlying active 2,4-pyrimidinediamine compound to be optimized for a particular mode of administration. It can also be selected to provide for removal at specified organs and/or tissues within the body, such as, for example, in the digestive tract, in blood and/or serum, or via enzymes residing in specific organs, such as the liver.

In some embodiments, progroups R^P that are phosphorous-containing progroups include phosphate moieties that can be cleaved in vitro by enzymes such as esterases, lipases and/or phosphatases. Such enzymes are prevalent throughout the body, residing in, for example, the stomach and digestive tract, blood and/or serum, and in virtually all tissues and organs. Such phosphate-containing progroups R^P will generally increase the water-solubility of the underlying active 2,4-pyrimidinediamine compound, making such phosphate-containing prodrugs ideally suited for modes of administration where water-solubility is desirable, such as, for example, oral, buccal, intravenous, intramuscular and ocular modes of administration.

In some embodiments, each phosphate-containing progroup R^P in the prodrug is of the formula —$(CR^dR^d)_y$—O—P(O)(OH)(OH), or a salt thereof, wherein R^d is as previously defined and y is an integer ranging from 1 to 3, typically 1 or 2. In one specific embodiment, each R^d is, independently of the others, selected from hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted methyl and substituted or unsubstituted benzyl. In another specific embodiment, each R^d is, independently of the others, selected from hydrogen and unsubstituted lower alkyl. Specific exemplary phosphate-containing progroups R^P include —CH_2—O—P(O)(OH)(OH) and —CH_2CH_2—O—P(O)(OH)(OH) and/or the corresponding salts.

While not intending to be bound by any theory of operation, when y is I in the exemplary phosphate-containing progroups R^P, it is believed that the phosphate-containing prodrugs are converted in vivo by enzymes such as phosphatases, lipases and/or esterases to the corresponding hydroxymethylamines, which are then further metabolized in vivo by the elimination of formaldehyde to yield the active 2,4-pyrimidinediamine drug compound. The phosphate and formaldehyde metabolic by-products are innocuous.

When y is 2 in the exemplary phosphate-containing prodrugs, it is believed that the prodrugs are metabolized to the active 2,4-pyrimidinediamine drug compound in vivo by elimination of enol phosphate, which further metabolizes to acetaldehyde and phosphate. The phosphate and acetaldehyde metabolic by-products are innocuous.

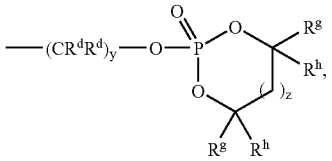
Skilled artisans will appreciate that certain types of precursors can be converted in vivo to phosphate groups. Such precursors include, by way of example and not limitation, phosphate esters, phosphites and phosphite esters. For example, phosphites can be oxidized in vivo to phosphates. Phosphate esters can be hydrolyzed in vivo to phosphates. Phosphite esters can be oxidized in vivo to phosphate esters, which can in turn be hydrolyzed in vivo to phosphates. As a consequence of the ability of these phosphate precursor groups to convert to phosphates in vivo, the prodrugs can also include progroups that comprise such phosphate precursors. In some embodiments, the phosphate precursor groups may be directly metabolized to the active 2,4-pyrimidinediamine drug, without first being converted into a phosphate prodrug. In other embodiments, prodrugs comprising progroups that include such phosphate precursors are first metabolized into the corresponding phosphate prodrug, which then metabolizes to the active 2,4-pyrimidinediamine drug via a hydroxymethylamine, as discussed above.

In some embodiments, such phosphate precursor groups are phosphate esters. The phosphate esters can be acyclic or cyclic, and can be phosphate triesters or phosphate diesters. Such esters are generally less water-soluble than the corresponding phosphate acid prodrugs and the corresponding active 2,4-pyrimidinediamine compounds, and are therefore typically suitable for modes of delivering prodrugs of active 2,4-pyrimidinediamine compounds where low water-solubility is desired, including, by way of example and not limitation, administration via inhalation. The solubility of the prodrug can be specifically tailored for specific modes of administration by appropriate selection of the number and identity(ies) of the esterifying groups in the phosphate ester.

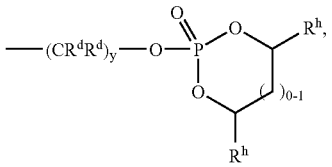
The mechanism by which the phosphate ester group metabolizes to the corresponding phosphate group can be controlled by appropriate selection of the esterifying moieties. For example, it is well-known that certain esters are acid (or base) labile, generating the corresponding phosphate under the acidic conditions found in the stomach and digestive tract. In instances where it is desirable for the phosphate ester prodrug to metabolize to the corresponding phosphate prodrug in the digestive tract (such as, for example, where the prodrugs are administered orally), phosphate ester progroups that are acid-labile can be selected. Other types of phosphate esters are acid and base stable, being converted into the corresponding phosphates via enzymes found in certain tissues and organs of the body (see, e.g., the various cyclic phosphate esters described in Erion et al., 2004, J. Am. Chem. Soc. 126:5154-5163, incorporated herein by reference). In instances where it is desirable to convert a phosphate ester prodrug into the corresponding phosphate prodrug within a desired target tissue or site within the body, phosphate esters having the desired metabolic properties can be selected.

In some embodiments, each phosphate ester-containing progroup R^P in the prodrug is an acyclic phosphate ester of the formula —$(CR^dR^d)_y$—O—P(O)(OH)(OR^e) or —$(CR^dR^d)_y$—O—P(O)(OR^e)(OR^e), or a salt thereof, wherein each R^e is, independently of the others, selected from substituted or unsubstituted lower alkyl, substituted or unsubstituted (C6-C14) aryl (e.g., phenyl, naphthyl, 4-loweralkoxyphenyl, 4-methoxyphenyl), substituted or unsubstituted (C7-C20) arylalkyl (e.g., benzyl, 1-phenylethan-1-yl, 2-phenylethan-1-yl), —$(CR^dR^d)_y$—OR^f, —$(CR^dR^d)_y$—O—C(O)R^f, —$(CR^dR^d)_y$—O—C(O)OR^f, —$(CR^dR^d)_y$—S—C(O)R^f, —$(CR^dR^d)_y$—S—C(O)OR^f, —$(CR^dR^d)_y$—NH—C(O)R^f, —$(CR^dR^d)_y$—NH—C(O)OR^f and —Si$(R^d)_3$, wherein R^d, R^f and y are as defined above. In a specific embodiment, each R^d is selected from hydrogen and unsubstituted lower alkyl and/or each R^e is an unsubstituted lower alkanyl or benzyl. Specific exemplary phosphate ester progroups include, but are not limited to, —CH_2—O—P(O)(OH)(OR^e), —CH_2CH_2—O—P(O)(OH)(OR^e), —CH_2—O—P(O)(OR^e)(OR^e) and —CH_2CH_2—O—P(O)(OR^e)(OR^e), where R^e is selected from lower alkanyl, i-propyl and t-butyl.

In other embodiments, each phosphate ester-containing progroup R^p is a cyclic phosphate ester of the formula

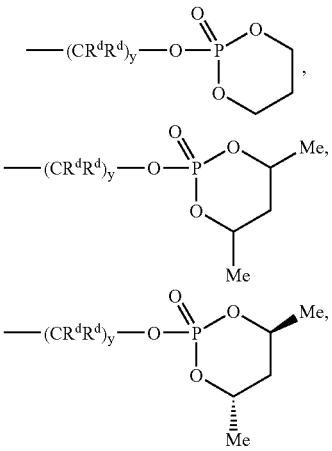


where each R^g is, independently of the others, selected from hydrogen and lower alkyl; each R^h is, independently of the others, selected from hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower cycloheteroalkyl, substituted or unsubstituted (C6-C14) aryl, substituted or unsubstituted (C7-C20) arylalkyl and substituted or unsubstituted 5-14 membered heteroaryl; z is an integer ranging from 0 to 2; and R^d and y are as previously defined. In a specific embodiment, each phosphate ester-containing progroup R^P is a cyclic phosphate ester of the formula



where R^d, R^h and y are as previously defined.

The mechanism by which cyclic phosphate ester prodrugs including such cyclic phosphate ester progroups metabolize in vivo to the active drug compound depends, in part, on the identity of the R^h substitutent. For example, cyclic phosphate ester progroups in which each R^h is, independently of the others, selected from hydrogen and lower alkyl are cleaved in vivo by esterases. Thus, in some embodiments, the cyclic phosphate ester progroups are selected such that they are cleavable in vivo by esterases. Specific examples of such cyclic phosphate ester progroups include, but are not limited to, progroups selected from



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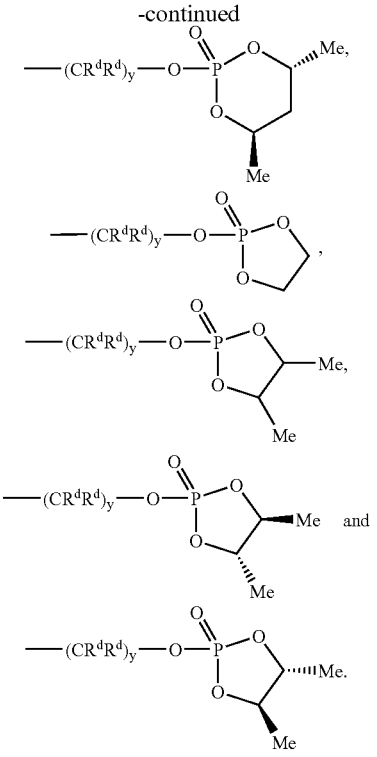
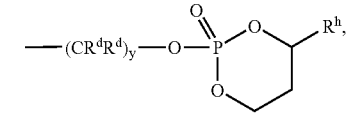


Alternatively, cyclic phosphate ester prodrugs having progroups in which the R^h substituents are substituted or unsubstituted aryl, arylalkyl and heteroaryl groups, are not typically cleaved by esterases, but are instead metabolized to the active prodrug by enzymes, such as cytochrome P_{450} enzymes, that reside in the liver. For example, a series of cyclic phosphate ester nucleotide prodrugs that undergo an oxidative cleavage reaction catalyzed by a cytochrome P_{450} enzyme (CYP) expressed predominantly in the liver are described in Erion et al., 2004, J. Am. Chem. Soc. 126:5154-5163. In some embodiments, the cyclic phosphate ester progroups are selected such that they are cleavable by CYP enzymes expressed in the liver. Specific exemplary embodiments of such cyclic phosphate ester-containing progroups R^p include, but are not limited to, progroups having the formula



where R^h is selected from phenyl, 3-chlorophenyl, 4-pyridyl and 4-methoxyphenyl.

As skilled artisans will appreciate, phosphites and phosphite esters can undergo oxidation in vivo to yield the corresponding phosphate and phosphate ester analogs. Such reactions can be carried out in vivo by, for example, oxidase enzymes, oxoreductase enzymes and other oxidative enzymes. Thus, the phosphorous-containing progroups R^p can also include phosphite and phosphite ester analogs of any of the phosphate and phosphate ester progroups described above. In some embodiments the phosphorous-containing progroups R^p include, but are not limited to, groups of the formula —$(CR^dR^d)_y$—O—P(OH)(OH), —$(CR^dR^d)_y$—O—

P(OH)(OR^e) and —(CR^{d}R^d)$_y$—O—P(OR^e)(R^e), or salts thereof, where R^d, R^e and y are as previously defined. Specific exemplary embodiments include groups in which each R^d is, independently of the others, selected from hydrogen and unsubstituted lower alkyl and/or each R^e is, independently of the others, selected from unsubstituted lower alkanyl and benzyl.

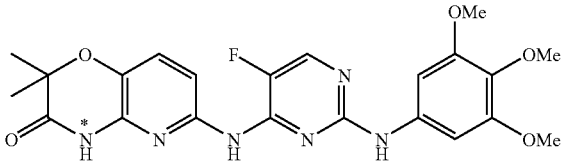
Specific exemplary acyclic phosphite and phosphite-ester progroups include, but are not limited to, —CH$_2$—O—P(OH)(OH), —CH$_2$CH$_2$—O—P(OH)(OH), —CH$_2$—O—P(OH)(OR^e), and —CH$_2$CH$_2$—O—P(OR)(OR^e), where each R^e is selected from lower alkanyl, i-propyl and t-butyl. Specific exemplary cyclic phosphite ester prodrugs include phosphite analogs of the above-described cyclic phosphate ester progroups. Conceptually, prodrug compounds including such phosphite and/or phosphite ester progroups can be thought of as prodrugs of the corresponding phosphate and phosphate ester prodrugs.

As mentioned above, it is believed that certain phosphate-containing prodrugs metabolize in vivo through the corresponding hydroxymethylamines. Although these hydroxymethylamines metabolize in vivo to the corresponding active 2,4-pyrimidinediamine compounds, they are stable at pH 7 and can be prepared and administered as hydroxyalkyl-containing prodrugs. In some embodiments, each hydroxyalkyl-containing progroup R^P of such prodrugs is of the formula —CR^{d}R^d—OH, where R^d is as previously defined. A specific exemplary hydroxyalkyl-containing progroup R^P is —CH$_2$OH.

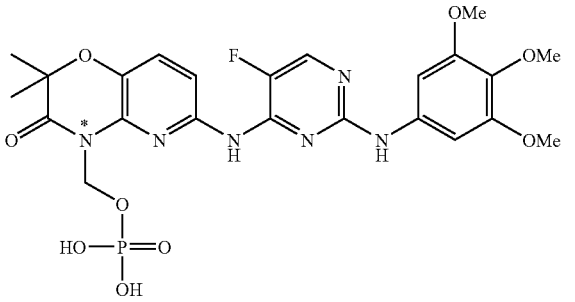
Virtually any known 2,4-pyrimidinediamine compound that has biological, and hence therapeutic, activity can be protected at an available primary or secondary amine with one or more progroups R^P as described herein. Suitable active 2,4-pyrimidinediamine compounds are described, for example, in U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Ser. No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893), the disclosures of which are incorporated herein by reference. In such 2,4-pyrimidinediamine compounds, the progroup(s) R^P can be attached to any available primary or secondary amine, including, for example, the N2 nitrogen atom of the 2,4-pyrimidinediamine moiety, the N4 nitrogen atom of the 2,4-pyrimidinediamine moiety, and/or a primary or secondary nitrogen atom included in a substituent on the 2,4-pyrimidinediamine compound. The use of phosphate-containing progroups R^P is especially useful for 2,4-pyrimidinediamine compounds that exhibit poor water solubility under physiological conditions (for example, solubilities of less than about 10 μg/ml). While not intending to be bound by any theory of operation, it is believed that the phosphate-containing progroups aid the solubility of the underlying active 2,4-pyrimidinediamine compound, which in turn increases its bioavailability when administered orally. It is believed that the phosphate progroups R^P are metabolized by phosphatase enzymes found in the digestive tract, permitting uptake of the underlying active drug.

It has been discovered that the water solubility and oral bioavailability of a particular biologically active 2,4-pyrimidinediamine compound, illustrated below (Compound 1), increased dramatically when formulated to include a progroup R^P of the formula —CH$_2$—O—P(O)(OH)$_2$ at the ring nitrogen atom highlighted with the asterisk (Compound 4):

Compound 1



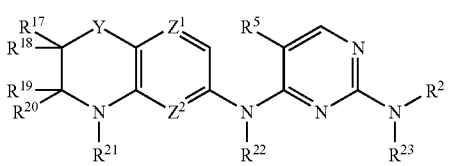
Compound 4



Significantly, whereas the water solubility of the active drug (Compound 1) is in the range of about 1-2 μg/ml in aqueous buffer under physiological conditions, the solubility of the corresponding phosphate prodrug (Compound 4) is greater than 5 mg/ml under the same conditions, or approximately 2000 times greater. This increased water-solubility allows for better dissolution in the gut, thereby facilitating oral administration. Other active 2,4-pyrimidinediamine compounds having similarly poor water solubilities are expected to exhibit similar increases in water solubility and oral bioavailability when formulated as phosphate prodrugs.

As mentioned above, phosphate ester prodrugs are generally less water-soluble than the corresponding phosphate prodrugs, and are therefore generally useful in applications where low water-solubility is desired, such as, for example, administration via inhalation. The same holds true for the relative water-solubility of phosphite ester and phosphite prodrugs.

In some embodiments, the prodrugs described herein are 2,4-pyrimidinediamine compounds that are substituted at the N4 nitrogen of the 2,4-pyrimidinediamine moiety with a substituted or unsubstituted nitrogen-containing bicyclic ring that includes at least one progroup R^P as described herein at one or more of: the nitrogen atom(s) of the bicyclic ring, he N2 nitrogen of the 2,4-pyrimidinediamine moiety and/or the N4 nitrogen of the 2,4-pyrimidinediamine moiety. In a specific illustrative exemplary embodiment, the prodrug is a compound according to structural formula (I):



(I)

including salts, solvates, hydrates and N-oxides thereof, wherein:

Y is selected from CH$_2$, NR^{24}, O, S, S(O) and S(O)$_2$;

Z^1 and Z^2 are each, independently of one another, selected from CH and N;

R^2 is an optionally substituted lower alkyl, lower cycloalkyl, lower heteroalkyl, lower cycloheteroalkyl, aryl, phenyl, or heteroaryl group;

R^5 is an electronegative group, such as, for example, a halo, fluoro, cyano, nitro, trihalomethyl or trifluoromethyl group;

R^{17} is selected from hydrogen, halogen, fluoro, lower alkyl and methyl or, alternatively, R^{17} may be taken together with $R1^8$ to form an oxo (=O) group or, together with the carbon atom to which they are attached, a spirocycle containing from 3 to 7 carbon atoms;

R^{18} is selected from hydrogen, halogen, fluoro, lower alkyl and methyl or, alternatively, R^{18} may be taken together with R^{17} to form an oxo (=O) group or, together with the carbon atom to which they are attached, a spirocycle containing from 3 to 7 carbon atoms;

R^{19} is selected from hydrogen, lower alkyl, and methyl or, alternatively, R^{19} may be taken together with R^{20} to form an oxo (=O) group or, together with the carbon atom to which they are attached, a spirocycle containing from 3 to 7 carbon atoms;

R^{20} is selected from hydrogen, lower alkyl and methyl or, alternatively, R^{20} may be taken together with R^{19} to form an oxo (=O) group or, together with the carbon atom to which they are attached, a spirocycle containing from 3 to 7 carbon atoms;

R^{21}, R^{22} and R^{23} are each, independently of one another, selected from hydrogen and a progroup R^P as described herein; and

R^{24} is selected from hydrogen, lower alkyl and a progroup R^P as described herein, with the proviso that at least one of R^{21}, R^{22}, R^{23} and R^{24} must be a progroup R^P. In some embodiments, each of R^{21}, R^{22} and R^{23} is one of the specific progroups exemplified above and R^{24} is hydrogen. In some embodiments R^{21} is one of the specific progroups exemplified above and R^{22}, R^{23} and R^{24} are each hydrogen. In some embodiments, R^{21}, R^{22} and R^{23} are each one of the specific progroups exemplified above and R^{24} is lower alkyl.

In another aspect, the present disclosure provides compositions comprising one or more of the prodrugs described herein and an appropriate carrier, excipient or diluent. The exact nature of the carrier, excipient or diluent will depend upon the desired use for the composition, and may range from being suitable or acceptable for veterinary uses to being suitable or acceptable for human use. The composition may optionally include one or more additional compounds.

In still another aspect, the present disclosure provides intermediates useful for synthesizing the prodrugs described herein. In the case of phosphate- or phosphite-containing prodrugs, the intermediates generally comprise prodrugs in which the oxygen atoms of the phosphate- and/or phosphite-containing progroups are masked with protecting groups that are selectively removable under specified conditions. In some embodiments, the protecting groups are selectively removable under mildly acidic conditions. In some embodiments, the intermediates are phosphate or phosphite esters which are themselves prodrugs that can be metabolized into active 2,4-pyrimidinediamine compounds. In one illustrative embodiment, the intermediates include prodrugs in which each R^P progroup is, independently of the others, of the formula $—(CR^dR^d)_y—O—P(O)(OR^i)(OR^i)$, $—(CR^dR^d)_y—O—P(O)(OR^i)(OH)$, $—(CR^dR^d)_y—O—P(OR^i)(OR^i)$ or $—(CR^dR^d)y-O—P(OR^i)(OH)$, where each R^i is, independently of the others, selected from lower unsubstituted alkanyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl, and R^d and y are as previously defined. In a specific embodiment, the intermediates include phosphate and/or phosphite esters in which each R^i is, independently of the others, selected from lower linear alkanyl, lower branched alkanyl, i-propyl, t-butyl and lower cyclic alkanyl.

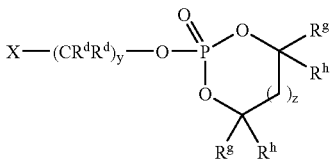
In some embodiments, the intermediates comprise an active 2,4-pyrimidinediamine that is substituted at a nitrogen atom of a primary or secondary amine group with a group of he formula $—CR^dR^d$-AH, where R^d and A are as previously defined.

In yet another aspect, the present disclosure provides methods of synthesizing the intermediates and/or prodrugs described herein. Phosphate-containing prodrugs can be synthesized by reacting an active 2,4-pyrimidinediamine compound with a phosphate ester halide, for example, a phosphate ester halide of the formula $X—(CR^dR^d)_y—O—P(O)(OR^j)(OR^j)$ or $X—(CR^dR^d)_y—O—P(O)(OR^j)(OH)$, where each R^j is, independently of the others, a selectively removable protecting group; X is a halide, such as, for example, chloride; and R^d and y are as previously defined. In some embodiments, each R^j is R^e, where as previously defined. Removal of the selectively removable protecting groups R^j yields a phosphate prodrug. In some embodiments each R^j is the same and is selected from lower linear alkyl, lower branched alkyl and lower cycloalkyl. In some embodiments, each R^j is isopropyl or t-butyl. In embodiments in which mixtures of intermediates are obtained, for example, mixtures of intermediates which contain different numbers of progroups or progroups at different positions on the 2,4-pyrimidinediamine molecule, the desired intermediate can be isolated from the mixture using standard separation and/or isolation techniques (e.g., column chromatography). Alternatively, a desired prodrug can be isolated from a mixture of different prodrugs using standard separation and/or isolation techniques.

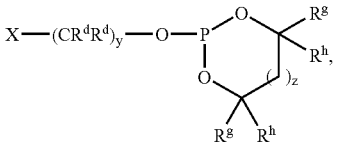
Acyclic phosphate ester prodrugs can be obtained in an analogous manner by reacting the active 2,4-pyrimidinediamine with a phosphate ester halide, for example a phosphate ester halide of the formula $X—(CR^dR^d)_y—O—P(O)(OH)(OR^e)$ or $X—(CR^dR^d)_y—O—P(O)(OR^e)(OR^e)$, where X, R^d, y and R^e are as previously defined. In this instance, removal of the esterifying groups R^e is not necessary.

Acyclic phosphite and phosphite ester prodrugs can be prepared in an analogous manner from the corresponding phosphite ester halides, for example phosphite ester halides of the formula $X—(CR^dR^d)_y—O—P(OR^j)(OR^j)$, $X—(CR^dR^d)_y—O—P(OR^e)(OH)$, $X—(CR^dR^d)_y—O—P(OR^e)(OR^e)$, where X, R^d, y, R^e and R^j are as previously defined.

Cyclic phosphate ester and phosphite ester prodrugs can be prepared by reacting the active 2,4-pyrimidinediamine compound with the corresponding cyclic phosphate ester or phosphite ester halide, for example, a cyclic phosphate ester halide of the formula



or a cyclic phosphite ester halide of the formula



where X, R^d, y, z, R^g and R^h are as previously defined.

Embodiments in which R^p is —CR^dR^d-AR^3 can be prepared from the corresponding 2,4-pyrimidinediamine drug using conventional methods. For example, when A is O, the intermediates can be synthesized by reacting an active 2,4-pyrimidinediamine compound, with an aldehyde or ketone of the formula R^d—C(O)—R^d, where R^d is as previously defined, to yield a corresponding hydroxymethylamine intermediate (where R^p is —CR^dR^d—OH). The hydroxymethylamine intermediate can then be converted into the prodrug using standard techniques. In accordance with the definition of R^p, the hydroxymethylamine intermediate is also a prodrug of the invention. For example, other drug substances containing secondary amines have been added to formaldehyde to afford their corresponding isolable hydroxymethylamine adducts, Bansal et al., *J. Pharmaceutical Sci.* 1981, 70: (8), 850-854; Bansal et al., *J. Pharmaceutical Sci.* 1981, 70: (8), 855-856; Khan et al., *J. Pharmaceutical and Biomedical Analysis* 1989, 7 (6), 685-691. Alternatively, hydroxyalkyl-containing prodrugs can be prepared in two steps by first reacting the active 2,4-pyrimidinediamine with a bis-functional electrophile, such as a halide of the formula X^1—CR^dR^d—X^2, where X^1 represents a first halide, X^2 represents a second halide and R^d is as previously defined. In a specific exemplary embodiment, the halide is of the formula I—CR^dR^d—Cl. The unreacted halide is then hydroxylated to yield the hydroxyalkyl-containing prodrug using standard techniques.

Prodrugs in which A is O, S or NR^{50} can be synthesized from corresponding N-methyl phosphate esters. According to this embodiment, the phosphate ester groups can be displaced with a group of the formula R^3-AH, where R^3 and A are as previously defined, to yield the prodrug, as discussed in further detail below.

Many of the prodrugs described herein, and in particular the prodrugs according to structural formula (I), metabolize to yield 2,4-pyrimidinediamine compounds that are potent inhibitors of degranulation of immune cells, such as mast, basophil, neutrophil and/or eosinophil cells. Additional 2,4-pyrimidinediamine compounds that exert similar biological activities that can be formulated as prodrugs as described herein and used in the various methods described herein are described in U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Ser. No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893), the disclosures of which are incorporated herein by reference. Thus, in still another aspect, the present disclosure provides methods of regulating, and in particular inhibiting, degranulation of such cells. The method generally involves contacting a cell that degranulates with an amount of a suitable prodrug described herein, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit degranulation of the cell. The method may be practiced in in vitro contexts provided that the contacting is performed under conditions in which the progroup(s) metabolize to yield the active 2,4-pyrimidinediamine compound, or in in vivo contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with cellular degranulation.

While not intending to be bound by any theory of operation, biochemical data confirm that many of these active 2,4-pyrimidinediamine compounds exert their degranulation inhibitory effect, at least in part, by blocking or inhibiting the signal transduction cascade(s) initiated by crosslinking of the high affinity Fc receptors for IgE ("FcεRI") and/or IgG ("FcγRI") (see, e.g., U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893), the disclosures of which are incorporated herein by reference. Indeed, these active 2,4-pyrimidinediamine compounds are potent inhibitors of both FcεRI-mediated and FcγRI-mediated degranulation. As a consequence, the prodrugs described herein may be used to inhibit these Fc receptor signaling cascades in any cell type expressing such FcεRI and/or FcγRI receptors including but not limited to macrophages, mast, basophil, neutrophil and/or eosinophil cells.

The methods also permit the regulation of, and in particular the inhibition of, downstream processes that result as a consequence of activating such Fc receptor signaling cascade(s). Such downstream processes include, but are not limited to, FcεRI-mediated and/or FcγRI-mediated degranulation, cytokine production and/or the production and/or release of lipid mediators such as leukotrienes and prostaglandins. The method generally involves contacting a cell expressing an Fc receptor, such as one of the cell types discussed above, with an amount of a prodrug described herein, or an acceptable salt, hydrate, solvent, N-oxide and/or composition thereof, effective to regulate or inhibit the Fc receptor signaling cascade and/or a downstream process effected by the activation of this signaling cascade. The method may be practiced in in vitro contexts provided that the contacting is performed under conditions under which the progroup(s) metabolize to yield the active 2,4-pyrimidinediamine compound, or in in vivo contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with the Fc receptor signaling cascade, such as diseases effected by the release of granule specific chemical mediators upon degranulation, the release and/or synthesis of cytokines and/or the release and/or synthesis of lipid mediators such as leukotrienes and prostaglandins.

In yet another aspect, the present disclosure provides methods of treating and/or preventing diseases characterized by, caused by or associated with the release of chemical mediators as a consequence of activating Fc receptor signaling cascades, such as FcεRI and/or FcγRI-signaling cascades. The methods may be practiced in animals in veterinary contexts or in humans. The methods generally involve administering to an animal subject or a human an amount of a prodrug described herein, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to treat or prevent the disease. As discussed previously, activation of the FcεRI or FcγRI receptor signaling cascade in certain immune cells leads to the release and/or synthesis of a variety of chemical substances that are pharmacological mediators of a

wide variety of diseases. Any of these diseases may be treated or prevented according to the methods of the invention.

For example, in mast cells and basophil cells, activation of the FcεRI or FcγRI signaling cascade leads to the immediate (i.e., within 1-3 min. of receptor activation) release of preformed mediators of atopic and/or Type I hypersensitivity reactions (e.g., histamine, proteases such as tryptase, etc.) via the degranulation process. Such atopic or Type I hypersensitivity reactions include, but are not limited to, anaphylactic reactions to environmental and other allergens (e.g., pollens, insect and/or animal venoms, foods, drugs, contrast dyes, etc.), anaphylactoid reactions, hay fever, allergic conjunctivitis, allergic rhinitis, allergic asthma, atopic dermatitis, eczema, urticaria, mucosal disorders, tissue disorders and certain gastrointestinal disorders.

The immediate release of the preformed mediators via degranulation is followed by the release and/or synthesis of a variety of other chemical mediators, including, among other things, platelet activating factor (PAF), prostaglandins and leukotrienes (e.g., LTC4) and the de novo synthesis and release of cytokines such as TNFα, IL-4, IL-5, IL-6, IL-13, etc. The first of these two processes occurs approximately 3-30 min. following receptor activation; the latter approximately 30 min.-7 hrs. following receptor activation. These "late stage" mediators are thought to be in part responsible for the chronic symptoms of the above-listed atopic and Type I hypersensitivity reactions, and in addition are chemical mediators of inflammation and inflammatory diseases (e.g., osteoarthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, idiopathic inflammatory bowel disease, irritable bowel syndrome, spastic colon, etc.), low grade scarring (e.g., scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction), and sicca complex or syndrome. All of these diseases may be treated or prevented according to the methods described herein.

Additional diseases that can be treated or prevented according to the methods described herein include diseases associated with basophil cell and/or mast cell pathology. Examples of such diseases include, but are not limited to, diseases of the skin such as scleroderma, cardiac diseases such as post myocardial infarction, pulmonary diseases such as pulmonary muscle changes or remodeling and chronic obstructive pulmonary disease (COPD), diseases of the gut such as inflammatory bowel syndrome (spastic colon), acute mycloid leukemia (AML) and immune thrombocytopenic purpura.

Many of the active 2,4-pyrimidinediamine compounds are also potent inhibitors of the tyrosine kinase Syk kinase. Examples of such 2,4-pyrimidinediamine are described, for example, in U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Ser. No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893), the disclosures of which are incorporated herein by reference. Thus, in still another aspect, the present disclosure provides methods of regulating, and in particular inhibiting, Syk kinase activity. The method generally involves contacting a Syk kinase or a cell comprising a Syk kinase with an amount of a suitable prodrug, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit Syk kinase activity. In one embodiment, the Syk kinase is an isolated or recombinant Syk kinase. In another embodiment, the Syk kinase is an endogenous or recombinant Syk kinase expressed by a cell, for example a mast cell or a basophil cell. The method may be practiced in in vitro contexts provided that the contacting is performed under conditions under which the progroup(s) metabolize to yield the active 2,4-pyrimidinediamine compound, or in in vivo contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with Syk kinase activity.

While not intending to be bound by any particular theory of operation, it is believed that such active 2,4-pyrimdinediamine compounds inhibit cellular degranulation and/or the release of other chemical mediators primarily by inhibiting Syk kinase that gets activated through the gamma chain homodimer of FcεRI. This gamma chain homodimer is shared by other Fc receptors, including FcγRI, FcγRIII and FcαRI. For all of these receptors, intracellular signal transduction is mediated by the common gamma chain homodimer. Binding and aggregation of those receptors results in the recruitment and activation of tyrosine kinases such as Syk kinase. As a consequence of these common signaling activities, the prodrugs described herein that metabolize to such active 2,4-pyrimidinediamine compounds may be used to regulate, and in particular inhibit, the signaling cascades of Fc receptors having this gamma chain homodimer, such as FcεRI, FcγRI, FcγRIII and FcαRI, as well as the cellular responses elicited through these receptors.

Syk kinase is known to play a critical role in other signaling cascades. For example, Syk kinase is an effector of B-cell receptor (BCR) signaling (Turner et al., 2000, Immunology Today 21:148-154) and is an essential component of integrin beta(1), beta(2) and beta(3) signaling in neutrophils (Mocsai et al., 2002, Immunity 16:547-558). Active 2,4-pyrimidinediamine compounds that are potent inhibitors of Syk kinase can be used to regulate, and in particular inhibit, any signaling cascade where Syk plays a role, such as, fore example, the Fc receptor, BCR and integrin signaling cascades, as well as the cellular responses elicited through these signaling cascades. Thus, the prodrugs described herein that metabolize to such active 2,4-pyrimidinediamine compounds can be used to regulate such activities. The particular cellular response regulated or inhibited will depend, in part, on the specific cell type and receptor signaling cascade, as is well known in the art. Non-limiting examples of cellular responses that may be regulated or inhibited with such prodrugs include a respiratory burst, cellular adhesion, cellular degranulation, cell spreading, cell migration, phagocytosis (e.g., in macrophages), calcium ion flux (e.g., in mast, basophil, neutrophil, eosinophil and B-cells), platelet aggregation, and cell maturation (e.g., in B-cells).

Thus, in another aspect, the present disclosure provides methods of regulating, and in particular inhibiting, signal transduction cascades in which Syk plays a role. The method generally involves contacting a Syk-dependent receptor or a cell expressing a Syk-dependent receptor with an amount of a suitable prodrug described herein, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit the signal transduction cascade. The methods may also be used to regulate, and in particular inhibit, downstream processes or cellular responses elicited by activation of the particular Syk-dependent signal transduction cascade. The methods may be practiced to regulate any signal transduction cascade where Syk is now known or later discovered to play a role. The methods may be practiced in in vitro contexts provided that the contacting is performed under conditions under which the progroup(s) metabolize to yield the active 2,4-pyrimidinediamine compound, or in in vivo

contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with activation of the Syk-dependent signal transduction cascade. Non-limited examples of such diseases include those previously discussed.

Recent studies have shown that activation of platelets by collagen is mediated through the same pathway used by immune receptors, with an immunoreceptor tyronsine kinase motif on the FcRγ playing a pivotal role (Watson & Gibbons, 1998, Immunol. Today 19:260-264), and also that FcRγ plays a pivotal role in the generation of neointimal hyperplasia following balloon injury in mice, most likely through collagen-induced activation of platelets and leukocyte recruitment (Konishi et al., 2002, Circulation 105:912-916). Thus, the prodrugs described herein can also be used to inhibit collagen-induced platelet activation and to treat or prevent diseases associated with or caused by such platelet activation, such as, for example, intimal hyperplasia and restenosis following vascular injury.

Cellular and animal data also confirm that many of these active 2,4-pyrimidinediamine compounds may also be used to treat or prevent autoimmune diseases and/or symptoms of such diseases (see, e.g., U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893), the disclosures of which are incorporated herein by reference. As a consequence, prodrugs of such active 2,4-pyrimidinediamine compounds can likewise be used to treat or prevent such autoimmune diseases and/or symptoms. The methods generally involve administering to a subject suffering from an autoimmune disease or at risk of developing an autoimmune disease an amount of a suitable prodrug described herein, or an acceptable salt, N-oxide, hydrate, solvate or composition thereof, effective to treat or prevent the autoimmune disease and/or its associated symptoms. Autoimmune diseases that can be treated or prevented with the prodrugs include those diseases that are commonly associated with nonanaphylactic hypersensitivity reactions (Type II, Type III and/or Type IV hypersensitivity reactions) and/or those diseases that are mediated, at least in part, by activation of the FcγR signaling cascade in monocyte cells. Such autoimmune disease include, but are not limited to, those autoimmune diseases that are frequently designated as single organ or single cell-type autoimmune disorders and those autoimmune disease that are frequently designated as involving systemic autoimmune disorder. Non-limiting examples of diseases frequently designated as single organ or single cell-type autoimmune disorders include: Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, ulcerative colitis and membranous glomerulopathy. Non-limiting examples of diseases often designated as involving systemic autoimmune disorder include: systemic lupus erythematosis, rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, multiple sclerosis and bullous pemphigoid. Additional autoimmune diseases, which can be β-cell (humoral) based or T-cell based, include autoimmune alopecia, Type I or juvenile onset diabetes, and thyroiditis.

5. BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** provides schemes illustrating metabolic pathways of exemplary phosphorous-containing prodrugs;

FIG. **2** provides a scheme illustrating a metabolic pathway of an exemplary cyclic phosphate ester prodrug;

FIG. **3** illustrates an exemplary synthesis of exemplary cyclic phosphate prodrug; and

FIGS. **4-11** provide graphs illustrating various pharmacokinetic data for drug Compound 1 and/or prodrug Compound 4.

6. DETAILED DESCRIPTION

6.1 Definitions

As used herein, the following terms are intended to have the following meanings:

"Alkyl" by itself or as part of another substituent refers to a saturated or unsaturated branched, straight-chain or cyclic monovalent hydrocarbon radical having the stated number of carbon atoms (i.e., C1-C6 means one to six carbon atoms) that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the like. Where specific levels of saturation are intended, the nomenclature "alkanyl," "alkenyl" and/or "alkynyl" is used, as defined below. As used herein, "lower alkyl" means (C1-C8) alkyl.

"Alkanyl" by itself or as part of another substituent refers to a saturated branched, straight-chain or cyclic alkyl derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, etc.; butanyls such as butan-1-yl, butan-2-yl (sec-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (t-butyl), cyclobutan-1-yl, etc.; and the like. As used herein, "lower alkanyl" means (C1-C8) alkanyl.

"Alkenyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the cis or trans conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl, prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl ; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, etc.; and the like. As used herein, "lower alkenyl" means (C2-C8) alkenyl.

"Alkynyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to,

ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the like. As used herein, "lower alkynyl" means (C2-C8) alkynyl.

"Alkyldiyl" by itself or as part of another substituent refers to a saturated or unsaturated, branched, straight-chain or cyclic divalent hydrocarbon group having the stated number of carbon atoms (i.e., C1-C6 means from one to six carbon atoms) derived by the removal of one hydrogen atom from each of two different carbon atoms of a parent alkane, alkene or alkyne, or by the removal of two hydrogen atoms from a single carbon atom of a parent alkane, alkene or alkyne. The two monovalent radical centers or each valency of the divalent radical center can form bonds with the same or different atoms. Typical alkyldiyl groups include, but are not limited to, methandiyl; ethyldiyls such as ethan-1,1-diyl, ethan-1,2-diyl, ethen-1,1 -diyl, ethen-1,2-diyl; propyldiyls such as propan-1,1 -diyl, propan-1,2-diyl, propan-2,2-diyl, propan-1,3-diyl, cyclopropan-1,1-diyl, cyclopropan-1,2-diyl, prop-1-en-1,1 -diyl, prop-1-en-1,2-diyl, prop-2-en-1,2-diyl, prop-1-en-1,3-diyl, cycloprop-1-en-1,2-diyl, cycloprop-2-en-1,2-diyl, cycloprop-2-en-1,1-diyl, prop-1-yn-1,3-diyl, etc.; butyldiyls such as, butan-1,1-diyl, butan-1,2-diyl, butan-1,3-diyl, butan-1,4-diyl, butan-2,2-diyl, 2-methyl-propan-1,1-diyl, 2-methyl-propan-1,2-diyl, cyclobutan-1,1-diyl; cyclobutan-1,2-diyl, cyclobutan-1,3-diyl, but-1-en-1,1-diyl, but-1-en-1,2-diyl, but-1-en-1,3-diyl, but-1-en-1,4-diyl, 2-methyl-prop-1-en-1,1 -diyl, 2-methanylidene-propan-1,1-diyl, buta-1,3-dien-1,1-diyl, buta-1,3-dien-1,2-diyl, buta-1,3-dien-1,3-diyl, buta-1,3-dien-1,4-diyl, cyclobut-1-en-1,2-diyl, cyclobut-1-en-1,3-diyl, cyclobut-2-en-1,2-diyl, cyclobuta-1,3-dien-1,2-diyl, cyclobuta-1,3-dien-1,3-diyl, but-1-yn-1,3-diyl, but-1-yn-1,4-diyl, buta-1,3-diyn-1,4-diyl, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkanyldiyl, alkenyldiyl and/or alkynyldiyl is used. Where it is specifically intended that the two valencies are on the same carbon atom, the nomenclature "alkylidene" is used. In some embodiments, the alkyldiyl group is (C1-C8) alkyldiyl. Specific embodiments include saturated acyclic alkanyldiyl groups in which the radical centers are at the terminal carbons, e.g., methandiyl (methano); ethan-1,2-diyl (ethano); propan-1,3-diyl (propano); butan-1,4-diyl (butano); and the like (also referred to as alkylenos, defined infra).

"Alkyleno" by itself or as part of another substituent refers to a straight-chain saturated or unsaturated alkyldiyl group having two terminal monovalent radical centers derived by the removal of one hydrogen atom from each of the two terminal carbon atoms of straight-chain parent alkane, alkene or alkyne. The locant of a double bond or triple bond, if present, in a particular alkyleno is indicated in square brackets. Typical alkyleno groups include, but are not limited to, methano; ethylenos such as ethano, etheno, ethyno; propylenos such as propano, prop[1]eno, propa[1,2]dieno, prop[1]yno, etc.; butylenos such as butano, but[1]eno, but[2]eno, buta[1,3]dieno, but[1]yno, but[2]yno, buta[1,3]diyno, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkano, alkeno and/or alkyno is used. In some embodiments, the alkyleno group is (C1-C8) or (C1-C3) alkyleno. Specific embodiments include straight-chain saturated alkano groups, e.g., methano, ethano, propano, butano, and the like.

"Heteroalkyl," Heteroalkanyl," Heteroalkenyl," Heteroalkynyl," Heteroalkyldiyl" and "Heteroalkyleno" by themselves or as part of another substituent refer to alkyl, alkanyl, alkenyl, alkynyl, alkyldiyl and alkyleno groups, respectively, in which one or more of the carbon atoms are each independently replaced with the same or different heteratoms or heteroatomic groups. Typical heteroatoms and/or heteroatomic groups which can replace the carbon atoms include, but are not limited to, —O—, —S—, —S—O—, —NR'—, —PH—, —S(O)—, —S(O)$_2$—, —S(O)NR'—, —S(O)$_2$NR'—, and the like, including combinations thereof, where each R' is independently hydrogen or (C1-C8) alkyl.

"Cycloalkyl" and "Heterocycloalkyl" by themselves or as part of another substituent refer to cyclic versions of "alkyl" and "heteroalkyl" groups, respectively. For heteroalkyl groups, a heteroatom can occupy the position that is attached to the remainder of the molecule. Typical cycloalkyl groups include, but are not limited to, cyclopropyl; cyclobutyls such as cyclobutanyl and cyclobutenyl; cyclopentyls such as cyclopentanyl and cyclopentenyl; cyclohexyls such as cyclohexanyl and cyclohexenyl; and the like. Typical heterocycloalkyl groups include, but are not limited to, tetrahydrofuranyl (e.g., tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, etc.), piperidinyl (e.g., piperidin-1-yl, piperidin-2-yl, etc.), morpholinyl (e.g., morpholin-3-yl, morpholin-4-yl, etc.), piperazinyl (e.g., piperazin-1-yl, piperazin-2-yl, etc.), and the like.

"Acyclic Heteroatomic Bridge" refers to a divalent bridge in which the backbone atoms are exclusively heteroatoms and/or heteroatomic groups. Typical acyclic heteroatomic bridges include, but are not limited to, —O—, —S—, —S—O—, —NR'—, —PH—, —S(O)—, —S(O)$_2$—, —S(O) NR'—, —S(O)$_2$NR'—, and the like, including combinations thereof, where each R' is independently hydrogen or (C1-C8) alkyl.

"Parent Aromatic Ring System" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "parent aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, tetrahydronaphthalene, etc. Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, tetrahydronaphthalene, triphenylene, trinaphthalene, and the like.

"Aryl" by itself or as part of another substituent refers to a monovalent aromatic hydrocarbon group having the stated number of carbon atoms (i.e., C6-C15 means from 6 to 15 carbon atoms) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, asindacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene, and the like, as well as the various hydro isomers thereof. In preferred embodiments, the aryl group is (C6-C15) aryl, with (C6-C10) being more typical. Specific exemplary aryls include phenyl and naphthyl.

"Arylaryl" by itself or as part of another substituent refers to a monovalent hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a ring system in which two or more identical or non-identical parent aromatic ring systems are joined directly together by a single bond, where the number of such direct ring junctions is one

less than the number of parent aromatic ring systems involved. Typical arylaryl groups include, but are not limited to, biphenyl, triphenyl, phenyl-naphthyl, binaphthyl, biphenyl-naphthyl, and the like. Where the number of carbon atoms in an arylaryl group are specified, the numbers refer to the carbon atoms comprising each parent aromatic ring. For example, (C6-C15) arylaryl is an arylaryl group in which each aromatic ring comprises from 6 to 15 carbons, e.g., biphenyl, triphenyl, binaphthyl, phenylnaphthyl, etc. In some embodiments, each parent aromatic ring system of an arylaryl group is independently a (C6-C15) aromatic, more preferably a (C6-C10) aromatic. Specific exemplary arylaryl groups include those in which all of the parent aromatic ring systems are identical, e.g., biphenyl, triphenyl, binaphthyl, trinaphthyl, etc.

"Biaryl" by itself or as part of another substituent refers to an arylaryl group having two identical parent aromatic systems joined directly together by a single bond. Typical biaryl groups include, but are not limited to, biphenyl, binaphthyl, bianthracyl, and the like. In some embodiments, the aromatic ring systems are (C6-C15) aromatic rings, more typically (C6-C10) aromatic rings. A particular exemplary biaryl group is biphenyl.

"Arylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylakenyl and/or arylalkynyl is used. In some embodiments, the arylalkyl group is (C7-C21) arylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C1-C6) and the aryl moiety is (C6-C15). In some specific embodiments the arylalkyl group is (C7-C13), e.g., the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C1-C3) and the aryl moiety is (C6-C10).

"Parent Heteroaromatic Ring System" refers to a parent aromatic ring system in which one or more carbon atoms are each independently replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups to replace the carbon atoms include, but are not limited to, N, NH, P, O, S, S(O), $S(O)_2$, Si, etc. Specifically included within the definition of "parent heteroaromatic ring systems" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, etc. Also included in the definition of "parent heteroaromatic ring system" are those recognized rings that include common substituents, such as, for example, benzopyrone and 1-methyl-1,2,3,4-tetrazole. Specifically excluded from the definition of "parent heteroaromatic ring system" are benzene rings fused to cyclic polyalkylene glycols such as cyclic polyethylene glycols. Typical parent heteroaromatic ring systems include, but are not limited to, acridine, benzimidazole, benzisoxazole, benzodioxan, benzodioxole, benzofuran, benzopyrone, benzothiadiazole, benzothiazole, benzotriazole, benzoxaxine, benzoxazole, benzoxazoline, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like.

"Heteroaryl" by itself or as part of another substituent refers to a monovalent heteroaromatic group having the stated number of ring atoms (e.g., "5-14 membered" means from 5 to 14 ring atoms) derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, benzimidazole, benzisoxazole, benzodioxan, benzodiaxole, benzofuiran, benzopyrone, benzothiadiazole, benzothiazole, benzotriazole, benzoxazine, benzoxazole, benzoxazoline, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like, as well as the various hydro isomers thereof. In preferred embodiments, the heteroaryl group is a 5-14 membered heteroaryl, with 5-10 membered heteroaryl being particularly preferred.

"Heteroaryl-Heteroarvl" by itself or as part of another substituent refers to a monovalent heteroaromatic group derived by the removal of one hydrogen atom from a single atom of a ring system in which two or more identical or non-identical parent heteroaromatic ring systems are joined directly together by a single bond, where the number of such direct ring junctions is one less than the number of parent heteroaromatic ring systems involved. Typical heteroaryl-heteroaryl groups include, but are not limited to, bipyridyl, tripyridyl, pyridylpurinyl, bipurinyl, etc. Where the number of atoms are specified, the numbers refer to the number of atoms comprising each parent heteroaromatic ring systems. For example, 5-15 membered heteroaryl-heteroaryl is a heteroaryl-heteroaryl group in which each parent heteroaromatic ring system comprises from 5 to 15 atoms, e.g., bipyridyl, tripuridyl, etc. In some embodiments, each parent heteroaromatic ring system is independently a 5-15 membered heteroaromatic, more typically a 5-10 membered heteroaromatic. Specific exemplary heteroaryl-heteroaryl groups include those in which all of the parent heteroaromatic ring systems are identical.

"Biheteroaryl" by itself or as part of another substituent refers to a heteroaryl-heteroaryl group having two identical parent heteroaromatic ring systems joined directly together by a single bond. Typical biheteroaryl groups include, but are not limited to, bipyridyl, bipurinyl, biquinolinyl, and the like. In some embodiments, the heteroaromatic ring systems are 5-15 membered heteroaromatic rings, more typically 5-10 membered heteroaromatic rings.

"Heteroarylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylakenyl and/or heteroarylalkynyl is used. In some embodiments, the heteroarylalkyl group is a 6-21 membered heteroarylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is (C1-C6) alkyl and the heteroaryl moiety is a 5-15-membered heteroaryl. In some specific exemplary embodiments, the heteroarylalkyl is a

6-13 membered heteroarylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety is (C1-C3) alkyl and the heteroaryl moiety is a 5-10 membered heteroaryl.

"Halogen" or "Halo" by themselves or as part of another substituent, unless otherwise stated, refer to fluoro, chloro, bromo and iodo.

"Haloalkyl" by itself or as part of another substituent refers to an alkyl group in which one or more of the hydrogen atoms is replaced with a halogen. Thus, the term "haloalkyl" is meant to include monohaloalkyls, dihaloalkyls, trihaloalkyls, etc. up to perhaloalkyls. For example, the expression "(C1-C2) haloalkyl" includes fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 1,1,1-trifluoroethyl, perfluoroethyl, etc.

The above-defined groups may include prefixes and/or suffixes that are commonly used in the art to create additional well-recognized substituent groups. As examples, "alkyloxy" or "alkoxy" refers to a group of the formula —OR", "alkylamine" refers to a group of the formula —NHR" and "dialkylamine" refers to a group of the formula —NR"R", where each R" is independently an alkyl. As another example, "haloalkoxy" or "haloalkyloxy" refers to a group of the formula —OR"', where R"' is a haloalkyl.

"Substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent(s). Substituent groups useful for substituting for hydrogens on saturated carbon atoms in the specified group or radical include, but are not limited to —R^{60}, halo, —O^-M^+, =O, —OR^{70}, —SR^{70}, —S^-M^+, =S, —$NR^{80}R^{80}$, =NR^{70}, =N—OR^{70}, trihalomethyl, —CF_3, —CN, —OCN, —SCN, —NO, —NO_2, =N_2, —N_3, —$S(O)_2R^{70}$, —$S(O)_2O^-M^+$, —$S(O)_2OR^{70}$, —$OS(O)_2R^{70}$, —$OS(O)_2O^-M^+$, —$OS(O)_2OR^{70}$, —$P(O)(O^-)_2(M^+)_2$, —$P(O)(OR^{70}O^-M^+$, —$P(O)(OR^{70})(OR^{70})$, —$C(O)R^{70}$, —$C(S)R^{70}$, —$C(NR^{70})R^{70}$, —$C(O)O^-M^+$, —$C(O)OR^{70}$, —$C(S)OR^{70}$, —$C(O)NR^{80}R^{80}$, —$C(NR^{70})NR^{80}R^{80}$, —OC(O)R^{70}, —$OC(S)R^{70}$, —$OC(O)O^-M^+$, —$OC(O)OR^{70}$, —$OC(S)OR^{70}$, —$NR^{70}C(O)R^{70}$, —$NR^{70}C(S)R^{70}$, —$NR^{70}C(O)O^-M^+$, —$NR^{70}C(O)OR^{70}$, —$NR^{70}C(S)OR^{70}$, —$NR^{70}C(O)NR^{80}R^{80}$, —$NR^{70}C(NR^{70})R^{70}$ and —$NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60} is selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; each R^{70} is independently hydrogen or R^{60}; each R^{80} is independently R^{70} or alternatively, the two R^{80}'s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered cycloheteroalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S; and each M^+ is a counter ion with a positive charge, for example, a positive charge independently selected from K^+, Na^+, $^+N(R^{60})_4$, and Li^+, or two of M^+, combine to form a divalent counterion, for example a divalent counterion selected from Ca^{2+}, Mg^{2+}, and Ba^{2+}. As specific examples, —$NR^{80}R^{80}$ is meant to include —NH_2, —NH-alkyl, N-pyrrolidinyl and N-morpholinyl.

Similarly, substituent groups useful for substituting for hydrogens on unsaturated carbon atoms in the specified group or radical include, but are not limited to, -R^{60}, halo, —O^-M^+, —OR^{70}, —SR^{70}, —S^-M^+, —$NR^{80}R^{80}$, trihalomethyl, —CF_3, —CN, —OCN, —SCN, —NO, —NO_2, —N_3, —$S(O)_2R^{70}$, —$S(O)_2O^-M^+$, —$S(O)_2OR^{70}$, —$OS(O)_2R^{70}$, —$OS(O)_2O^-M^+$, —$OS(O)_2OR^{70}$, —$P(O)(O^-)_2(M^+)_2$, —$P(O)(OR^{70})O^-M^+$, —$P(O)(OR^{70})(OR^{70})$, —$C(O)R^{70}$, —$C(S)R^{70}$, —$C(NR^{70})R^{70}$, —$C(O)O^-M^+$, —$C(O)OR^{70}$, —$C(S)OR^{70}$, —$C(O)NR^{80}R^{80}$, —$C(NR^{70})NR^{80}R^{80}$, —OC(O)R^{70}, —$OC(S)R^{70}$, —$OC(O)O^-M^+$, —$OC(O)OR^{70}$, —$OC(S)OR^{70}$, —$NR^{70}C(O)R^{70}$, —$NR^{70}C(S)R^{70}$, —$NR^{70}C(O)O^-M^+$, —$NR^{70}C(O)OR^{70}$, —$NR^{70}C(S)OR^{70}$, —$NR^{70}C(O)NR^{80}R^{80}$, —$NR^{70}C(NR^{70})R^{70}$ and —$NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M^+ are as previously defined.

Substituent groups, other than R^p, useful for substituting for hydrogens on nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, but are not limited to, —R^{60}, —O^-M^+, —OR^{70}, —SR^{70}, —S^-M^+, —$NR^{80}R^{80}$, trihalomethyl, —CF_3, —CN, —NO, —NO_2, —$S(O)_2R^{70}$, —$S(O)_2O^-M^+$, —$S(O)_2OR^{70}$, —$OS(O)_2R^{70}$, —$OS(O)_2O^-M^+$, —$OS(O)_2OR^{70}$, —$P(O)(O^-)_2(M^+)_2$, —$P(O)(OR^{70})O^-M^+$, —$P(O)(OR^{70})(OR^{70})$, —$C(O)R^{70}$, —$C(S)R^{70}$, —$C(NR^{70})R^{70}$, —$C(O)OR^{70}$, —$C(S)OR^{70}$, —$C(O)NR^{80}R^{80}$, —$C(NR^{70})NR^{80}R^{80}$, —OC(O)R^{70}, —$OC(S)R^{70}$, —$OC(O)OR^{70}$, —$OC(S)OR^{70}$, —$NR^{70}C(O)R^{70}$, —$NR^{70}C(S)R^{70}$, —$NR^{70}C(O)OR^{70}$, —$NR^{70}C(NR^{70})R^{70}$ and —$NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M^+ are as previously defined.

Substituent groups from the above lists useful for substituting other groups or atoms specified as "substituted" will be apparent to those of skill in the art.

"Protecting group" refers to a group of atoms that, when attached to a reactive finctional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry,* 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, New York. Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPPS groups) and allyl ethers.

"Fc Receptor" refers to a member of the family of cell surface molecules that binds the Fc portion (containing the specific constant region) of an immunoglobulin. Each Fc receptor binds immunoglobulins of a specific type. For example the Fcα receptor ("FcαR") binds IgA, the FcεR binds IgE and the FcγR binds IgG.

The FcαR family includes the polymeric Ig receptor involved in epithelial transport of IgA/IgM, the mycloid specific receptor RcαRI (also called CD89), the Fcα/μR and at least two alternative IgA receptors (for a recent review see Monteiro & van de Winkel, 2003, Annu. Rev. Immunol, advanced e-publication). The FcαRI is expressed on neutrophils, eosinophils, monocytes/macrophages, dendritic cells and kupfer cells. The FcαRI includes one alpha chain and the FcR gamma homodimer that bears an activation motif (ITAM) in the cytoplasmic domain and phosphorylates Syk kinase.

The FcεR family includes two types, designated FcεRI and FcεRII (also known as CD23). FcεRI is a high affinity receptor (binds IgE with an affinity of about $10^{10}M^{-1}$) found on mast, basophil and eosinophil cells that anchors monomeric IgE to the cell surface. The FcεRI possesses one alpha chain, one beta chain and the gamma chain homodimer discussed above. The FcεRII is a low affinity receptor expressed on

mononuclear phagocytes, B lymphocytes, eosinophils and platelets. The FcεRII comprises a single polypeptide chain and does not include the gamma chain homodimer.

The FcγR family includes three types, designated FcγRI (also known as CD64), FcγRII (also known as CD32) and FcγRIII (also known as CD16). FcγRI is a high affinity receptor (binds IgG1 with an affinity of 10^8M^{-1}) found on mast, basophil, mononuclear, neutrophil, eosinophil, dendritic and phagocyte cells that anchors nomomeric IgG to the cell surface. The FcγRI includes one alpha chain and the gamma chain dimer shared by FcαRI and FcεRI.

The FcγRII is a low affinity receptor expressed on neutrophils, monocytes, eosinophils, platelets and B lymphocytes. The FcγRII includes one alpha chain, and does not include the gamma chain homodimer discussed above.

The FcγRIII is a low affinity (binds IgGI with an affinity of $5\times10^5M^{-1}$) expressed on NK, eosinophil, macrophage, neutrophil and mast cells. It comprises one alpha chain and the gamma homodimer shared by FcαRI, FcεRI and FcγRI.

Skilled artisans will recognize that the subunit structure and binding properties of these various Fc receptors, as well as the cell types expressing them, are not completely characterized. The above discussion merely reflects the current state-of-the-art regarding these receptors (see, e.g., Immunobiology: The Immune System in Health & Disease, 5^{th} Edition, Janeway et al., Eds, 2001, ISBN 0-8153-3642-x, FIG. 9.30 at pp. 371), and is not intended to be limiting with respect to the myriad receptor signaling cascades that can be regulated with the prodrugs described herein.

"Fc Receptor-Mediated Degranulation" or "Fc Receptor-Induced Degranulation" refers to degranulation that proceeds via an Fc receptor signal transduction cascade initiated by crosslinking of an Fc receptor.

"IgE-Induced Degranulation" or "FcεRI-Mediated Degranulation" refers to degranulation that proceeds via the IgE receptor signal transduction cascade initiated by crosslinking of $Fc\varepsilon R^p$ -bound IgE. The crosslinking may be induced by an IgE-specific allergen or other multivalent binding agent, such as an anti-IgE antibody. In mast and/or basophil cells, the FcεRI signaling cascade leading to degranulation may be broken into two stages: upstream and downstream. The upstream stage includes all of the processes that occur prior to calcium ion mobilization. The downstream stage includes calcium ion mobilization and all processes downstream thereof. Compounds that inhibit FcεRI-mediated degranulation may act at any point along the FcεRI-mediated signal transduction cascade. Compounds that selectively inhibit upstream FcεRI-mediated degranulation act to inhibit that portion of the FcεRI signaling cascade upstream of the point at which calcium ion mobilization is induced. In cell-based assays, compounds that selectively inhibit upstream FcεRI-mediated degranulation inhibit degranulation of cells such as mast or basophil cells that are activated or stimulated with an IgE-specific allergen or binding agent (such as an anti-IgE antibody) but do not appreciably inhibit degranulation of cells that are activated or stimulated with degranulating agents that bypass the FcεRI signaling pathway, such as, for example the calcium ionophores ionomycin and A23187.

"IgG-Induced Degranulation" or "FcγRI-Mediated Degranulation" refers to degranulation that proceeds via the FcγRI signal transduction cascade initiated by crosslinking of FcγRI-bound IgG. The crosslinking may be induced by an IgG-specific allergen or another multivalent binding agent, such as an anti-IgG or fragment antibody. Like the FcεRI signaling cascade, in mast and basophil cells the FcγRI signaling cascade also leads to degranulation which may be broken into the same two stages: upstream and downstream. Similar to FcεRI-mediated degranulation, compounds that selectively inhibit upstream FcγRI-mediated degranulation act upstream of the point at which calcium ion mobilization is induced. In cell-based assays, compounds that selectively inhibit upstream FcγRI-mediated degranulation inhibit degranulation of cells such as mast or basophil cells that are activated or stimulated with an IgG-specific allergen or binding agent (such as an anti-IgG antibody or fragment) but do not appreciably inhibit degranulation of cells that are activated or stimulated with degranulating agents that bypass the FcγRI signaling pathway, such as, for example the calcium ionophores ionomycin and A23187.

"Ionophore-Induced Degranulation" or "Ionophore-Mediated Degranulation" refers to degranulation of a cell, such as a mast or basophil cell, that occurs upon exposure to a calcium ionophore such as, for example, ionomycin or A23187.

"Syk Kinase" refers to the well-known 72 kDa non-receptor (cytoplasmic) spleen protein tyrosine kinase expressed in B-cells and other hematopoetic cells. Syk kinase includes two consensus Src-homology 2 (SH2) domains in tandem that bind to phosphorylated immunoreceptor tyrosine-based activation motifs ("ITAMs"), a "linker" domain and a catalytic domain (for a review of the structure and function of Syk kinase see Sada et al., 2001, J. Biochem. (Tokyo) 130:177-186); see also Turner et al., 2000, Immunology Today 21:148-154). Syk kinase has been extensively studied as an effector of B-cell receptor (BCR) signaling (Turner et al., 2000, supra). Syk kinase is also critical for tyrosine phosphorylation of multiple proteins which regulate important pathways leading from immunoreceptors, such as Ca^{2+} mobilization and mitogen-activated protein kinase (MAPK) cascades and degranulation. Syk kinase also plays a critical role in integrin signaling in neutrophils (see, e.g., Mocsai et al. 2002, Immunity 16:547-558).

As used herein, Syk kinase includes kinases from any species of animal, including but not limited to, homosapiens, simian, bovine, porcine, rodent, etc., recognized as belonging to the Syk family. Specifically included are isoforms, splice variants, allelic variants, mutants, both naturally occurring and man-made. The amino acid sequences of such Syk kinases are well known and available from GENBANK. Specific examples of mRNAs encoding different isoforms of human Syk kinase can be found at GENBANK accession no. gi|21361552|ref|NM_003177.2|, gi|496899|emb|Z29630.1|HSSYKPTK[496899] and gi|15030258|gb|BC011399.1|BC011399[15030258], which are incorporated herein by reference.

Skilled artisans will appreciate that tyrosine kinases belonging to other families may have active sites or binding pockets that are similar in three-dimensional structure to that of Syk. As a consequence of this structural similarity, such kinases, referred to herein as "Syk mimics," are expected to catalyze phosphorylation of substrates phosphorylated by Syk. Thus, it will be appreciated that such Syk mimics, signal transduction cascades in which such Syk mimics play a role, and biological responses effected by such Syk mimics and Syk mimic-dependent signaling cascades may be regulated, and in particular inhibited, with many of the prodrugs described herein.

"Syk-Dependent Signaling Cascade" refers to a signal transduction cascade in which Syk kinase plays a role. Non-limiting examples of such Syk-dependent signaling cascades include the FcαRI, FcεRI, FcγRI, FcγRIII, BCR and integrin signaling cascades.

"Autoimmune Disease" refers to those diseases which are commonly associated with the nonanaphylactic hypersensi-

tivity reactions (Type II, Type III and/or Type IV hypersensitivity reactions) that generally result as a consequence of the subject's own humoral and/or cell-mediated immune response to one or more immunogenic substances of endogenous and/or exogenous origin. Such autoimmune diseases are distinguished from diseases associated with the anaphylactic (Type I or IgE-mediated) hypersensitivity reactions.

6.2 The Prodrug Compounds

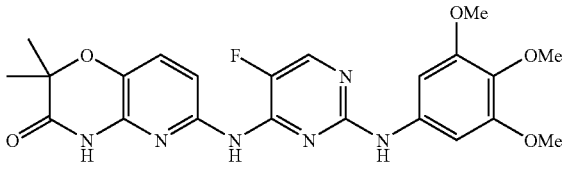
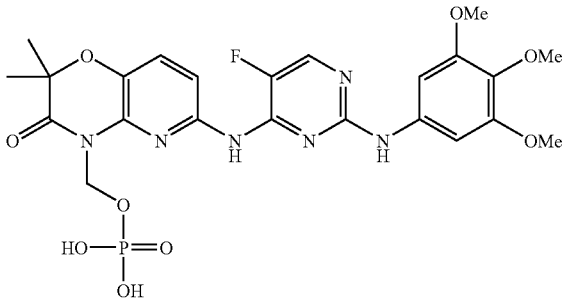
As described in the Summary, the instant disclosure provides prodrugs of biologically active 2,4-pyrimidinediamine compounds, such as the various 2,4-pyrimidinediamine compounds described in U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Ser. No. PCT/U503/03022 filed Jan.31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893), the disclosures of which are incorporated herein by reference. Prodrugs of these 2,4-pyrimidinediamine compounds are of particular interest, as these compounds inhibit upstream Fc receptor signaling cascades as well as Syk kinase and Syk kinase-dependent signaling cascades. The prodrugs generally include such active 2,4-pyrimidinediamine compounds in which one or more of the available primary or secondary amine groups is masked with a progroup R^p that metabolizes in vivo by to yield the active 2,4 pyrimidinediamine drug. As also discussed in the Summary section, and as will be discussed in more detail, below, the nature of the progroup can vary, and will depend upon, among other factors, the desired water solubility of the prodrug, its intended mode of administration and/or its intended mechanism or site of metabolism to the active 2,4-pyrimidinediamine compound.

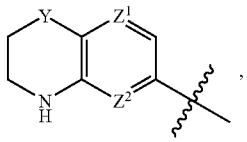
For example, it has been discovered that a specific active 2,4-pyrimidinediamine drug (Compound 1, below), exhibits vastly superior water solubility when formulated as a phosphate prodrug (Compound 4, below):

This prodrug Compound 4 also exhibits superior bioavailability compared to the corresponding active drug Compound 1 when administered orally to test animals. In fact, unlike the drug Compound 1, absorption of the prodrug Compound 4 is not dependent upon formulation. In pharmacokinetics studies carried out in rats, the prodrug Compound 4 was absorbed equally well from solutions (e.g., PEG-400 solutions and carboxymethylcellulose solutions) and powders (packed in hard gelatin capsules). While not intending to be bound by any particular theory of operation, it is believed that the improved oral bioavailability of the prodrug Compound 4, as well as its formulation-independent absorption, is due, at least in part, to its higher water-solubility. It is expected that other active 2,4-pyrimidinediamine compounds that have similarly low water solubilities, and hence oral bioavailabilities, will exhibit similar increases in water solubility and oral bioavailability when formulated as phosphate prodrugs.

Conversely, the corresponding phosphate ester prodrug of active drug Compound 1 would be expected to have lower water-solubility than the active Compound 1 compound. Thus, it is expected that phosphate ester prodrugs of active 2,4-pyrimidinediamine compounds that have lower water-solubility than the corresponding active 2,4-pyrimidinediamine compounds will be especially useful in applications and formulations where low water-solubility is desirable, such as formulations adapted for delivery via inhalation.

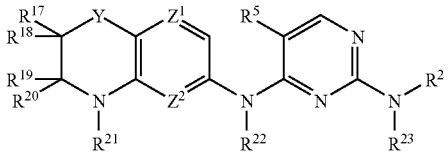
One class of active 2,4-pyrimidinediamine compounds that is expected to benefit from formulation as prodrugs, and in particular as phosphate prodrugs, includes 2,4-pyrimidinediamines in which the N4-substituent of the 2,4-pyrimidinediamine moiety is a substituted or unsubstituted nitrogen-containing heteroaryl ring of the formula

Compound	Structure	Solubility
Compound 1		1-2 μg/ml
Compound 4		>5 mg/ml



where Z^1 and Z^2 are each, independently of one another, selected from CH and N and Y is selected from CH_2, NH, O, S, S(O) and $S(O)_2$. Such prodrugs can include progroups R^P at: one or both of the non-aromatic ring nitrogens of the heteroaryl ring, the N2-nitrogen of the 2,4-pyrimidinediamine moiety, the N4-nitrogen atom of the 2,4-pyrimidinediamine moiety and/or any available nitrogen atoms in the substituent attached to the N2 nitrogen atom of the 2,4-pyrimidinediamine moiety.

In one illustrative embodiment, the prodrugs are compounds according to structural formula (I):



(I)

including salts, solvates, hydrates and N-oxides thereof, wherein:

Y is selected from CH_2, NR^{24}, O, S, S(O) and $S(O)_2$;

Z^1 and Z^2 are each, independently of one another, selected from CH and N;

R^2 is selected from lower alkyl optionally substituted with one or more of the same or different R^8 groups, lower cycloalkyl optionally substituted with one or more of the same or different R groups, cyclohexyl optionally substituted with one or more of the same or different R8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C6-C14) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from halo, fluoro, cyano, nitro, trihalomethyl and trifluoromethyl;

R^8 is selected from R^a, R^b, R^a substituted with one or more, for example, from one to four, of the same or different R^a or R^b, —OR^a substituted with one or more of the same or different R^a or R^b, —$B(OR^a)_2$, —$B(NR^cR^c)_2$, —$(CH_2)_m$—R^b, —$(CHR^a)_m$—R^b, —O—$(CH_2)_m$—R^b, —S—$(CH_2)_m$—R^b, —O—CHR^aR^b, —O—$CR^a(R^b)_2$, —O—$(CHR^a)_m$—R^b, —O—$(CH_2)_m$—$CH[(CH_2)_mR^b]R^b$, —S—$(CHR^a)_m$—R^b, —C(O)NH—$(CH_2)_m$—R^b, —C(O)NH—$(CHR^a)_m$—R^b, —O—$(CH_2)_m$—C(O)NH—$(CH_2)_m$—R^b, —S—$(CH_2)_m$—C(O)NH—$(CH_2)_m$—R^b, —O—$(CHR^a)_m$—C(O)NH—$(CHR^a)_m$—R^b, —S—$(CHR^a)_m$—C(O)NH—$(CHR^a)_m$—R^b, —NH—$(CH_2)_m$—R^b, —NH—$(CHR^a)_m$—R^b, —NH—$[(CH_2)_m$ $R^b]$, —N—$[(CH_2)_mR^b]_2$, —NH—C(O)—NH—$(CH_2)_m$ —R^b, —NH—C(O)—$(CH_2)_m$—CHR^bR^b and —NH—$(CH_2)_m$—C(O)—NH—$(CH_2)_m$—R^b;

R^{17} is selected from hydrogen, halogen, fluoro, lower alkyl and methyl or, alternatively, R^{17} may be taken together with R^{18} to form an oxo (=O) group or, together with the carbon atom to which they are attached, a spirocycle containing from 3 to 7 carbon atoms;

R^{18} is selected from hydrogen, halogen, fluoro, lower alkyl and methyl or, alternatively, R^{18} may be taken together with R^{17} to form an oxo (=O) group or, together with the carbon atom to which they are attached, a spirocycle containing from 3 to 7 carbon atoms;

R^{19} is selected from hydrogen, lower alkyl, and methyl or, alternatively, R^{19} may be taken together with R^{20} to form an oxo (=O) group or, together with the carbon atom to which they are attached, a spirocycle containing from 3 to 7 carbon atoms;

R^{20} is selected from hydrogen, lower alkyl and methyl or, alternatively, R^{20} may be taken together with R^{19} to form an oxo (=O) group or, together with the carbon atom to which they are attached, a spirocycle containing from 3 to 7 carbon atoms;

each R^a is, independently of the others, selected from hydrogen, lower alkyl, lower cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C6-C10) aryl, phenyl, (C7-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from =O, —OR^a, (C1-C3) haloalkyloxy, =S, —SR^a, =NR^a, =NOR^a, —NR^cR^c, halogen, —CF_3, —CN, —NC, —OCN, —SCN, —NO, —NO_2, =N_2, —N_3, —$S(O)R^a$, —$S(O)_2R^a$, —$S(O)_2OR^a$, $S(O)NR^cR^c$, —$S(O)_2NR^cR^c$, —$OS(O)R^a$, —$OS(O)_2R^a$, —$OS(O)_2OR^a$, —$OS(O)_2NR^cR^c$, —$C(O)R^a$, —$C(O)OR^a$, —$C(O)NR^cR^c$, —$C(NH)NR^cR^c$, —$C(NR^a)NR^cR^c$, —$C(NOH)R^a$, —$C(NOH)NR^cR^c$, —$OC(O)R^a$, —$OC(O)OR^a$, $OC(O)NR^cR^c$, —$OC(NH)NR^cR^c$, —$OC(NR^a)NR^cR^c$, —$[NHC(O)]_nR^a$, —$[NR^aC(O)]_nR^a$, —$[NHC(O)]_nOR^a$, —$[NR^aC(O)]_nOR^a$, —$[NHC(O)]_nNR^cR^c$, —$[NR^aC(O)]_nNR^cR^c$, —$[NHC(NH)]_nNR^cR^c$ and —$[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is, independently of the others, selected from a protecting group and R^a, or, alternatively, the two R^c bonded to the same nitrogen atom are taken together with that nitrogen atom to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which may optionally be substituted with one or more, for example, from one to four, of the same or different R^a groups;

R^{21}, R^{22} and R^{23} are each, independently of one another, selected from hydrogen and a progroup R^P;

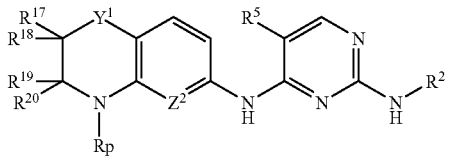
R^{24} is selected from hydrogen, lower alkyl and progroup R^P;

each m is, independently of the others, an integer from 1 to 3; and

each n is, independently of the others, an integer from 0 to 3, with the proviso that at least one of R^{21}, R^{22}, R^{23} and R^{24} is a progroup.

In the prodrugs described herein, and in particular in the prodrugs of structural formula (I), R^{21}, R^{22} and R^{23} each represent either hydrogen or a progroup R^P. Also, R^{24} represents hydrogen, a lower alkyl or a progroup R^P. Thus, the prodrugs can include a single R^P progroup, two R^P progroups, three R^P progroups, or even more R^P progroups, depending, in part, on the identity of Y and whether the R^2 substituent includes any R^P progroups. In some embodiments, it is preferred that the prodrugs described herein, and in particular the prodrugs of structural formula (I), include only one R^P group. Without intending to be bound by any theory of operation, it is possible that the different R^P groups in prodrugs including

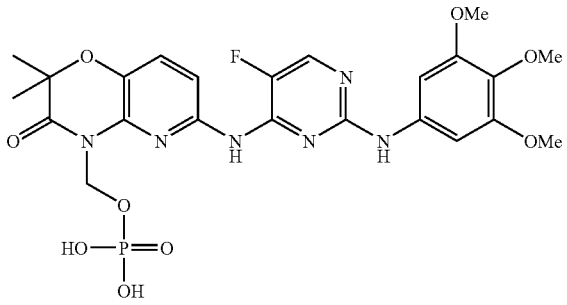
more than one R^P progroup may metabolize at different rates. Prodrugs including a single R^P progroup would avoid such differential metabolic kinetics. A specific embodiment of prodrugs according to structural formula (I) that include a single progroup R^P are compounds according to structural formula (Ia):



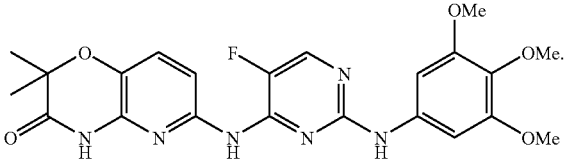
(Ia)

wherein Y^1 is selected from CH_2, NR^{24}, O, S, S(O) and $S(O)_2$; and Z^2, R^2, R^5, R^{17}, R^{18}, R^{19}, R^{20}, R^{24} and R^P are as previously defined, with the proviso that R^2 does not include any R^P groups.

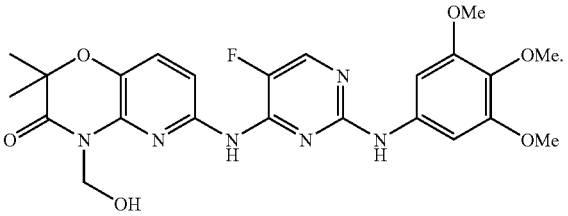
The identity of any R^P progroups present in the prodrugs described herein is not critical for success, provided that it hydrolyzes under the conditions of use to yield the active 2,4-pyrimidinediamine compound. It has recently been discovered that a phosphate-containing prodrug according to the structure illustrated below:



metabolizes in vivo to the corresponding active 2,4-pyrimidinediamine compound (Compound 1), illustrated below:



While not intending to be bound by any particular theory operation, it is believed that this prodrug metabolizes to active Compound 1 via the corresponding hydroxymethylamine intermediate illustrated below:



Such hydroxymethylamine compound are known to be unstable under physiological conditions and various pH ranges where they hydrolyze in vivo to yield formaldehyde and the active drug substance. Based on this observation, it is believed that prodrugs that include hydroxyl "protecting" groups that can be metabolized in vivo, for example by the acidic conditions of the stomach and/or by enzymes present in the digestive tract or other organs and/or tissues or fluids with the body, to yield the hydroxymethylamine intermediate illustrated above will likewise metabolize to the active 2,4 pyrimidinediamine drug.

Moreover, it is expected that the amino and thio analogs of this hydroxymethylamine intermediate, will be similarly unstable at physiological conditions and also hydrolyze in vivo to the active 2,4-pyrimidinediamine drug. Accordingly, it is also expected that the corresponding amino and thio compounds, as well as compounds in which the α-amino and α-thio groups are masked with "protecting" groups that are removed under physiological conditions of use to yield the α-amino and α-thio groups, will likewise make suitable prodrugs.

Thus, in some embodiments, the progroup(s) R^p in the prodrugs of structural formulae (I) and (Ia) are of the formula $—CR^dR^d\text{-}A\text{-}R^3$, where each R^d is, independently of the other, selected from hydrogen, cyano, $—C(O)R^e$, $—C(O)OR^e$, $—C(O)NR^eR^e$, $—C(OR^e)(OR^e)$, optionally substituted (C1-C20) alkyl, (C1-C20) perfluoroalkyl, optionally substituted (C7-C30) arylalkyl and optionally substituted 6-30 membered heteroarylalkyl, where each R^e is, independently of the others, selected from hydrogen, alkyl (for example lower alkyl), aryl (for example phenyl or naphthyl, arylalkyl (for example benzyl), heteroaryl and heteroarylalkyl; A is selected from O, S and NR^{50}, where R^{50} is selected from R^d and cycloalkyl, or, alternatively, is taken together with R^3 such that R^{50} and R^3, together with nitrogen atom to which they are attached, form a three-to seven-membered ring; and $R^3$is a group that, together with A, metabolizes under the conditions of use to yield an intermediate group of the formula $—CR^dR^dAH$, where R^d and A are as previously defined. As mentioned above, compounds of structural formula (I) and (Ia) in which the R^p groups are of the formula $—CR^dR^d\text{-}AH$ spontaneously hydrolyze in vivo to yield the active 2,4-pyrimidinediamine drug.

The mechanism by which the R^3 group metabolizes to yield intermediate group $—CR^dR^d\text{-}A\text{-}H$ is not critical, and can be caused by, for example, hydrolysis under the acidic

conditions of the stomach, and/or by enzymes present in the digestive tract and/or tissues or organs of the body. Indeed, the R^3 group(s) can be selected to metabolize at a particular site within the body. For example, many esters are cleaved under the acidic conditions found in the stomach. Prodrugs designed to cleave chemically in the stomach to the active 2,4-pyrimidinediamine can employ progroups including such esters. Alternatively, the progroups may be designed to metabolize in the presence of enzymes such as esterases, amidases, lipolases, phosphatases including ATPases and kinase etc., to yield the intermediate group of formula —CR^dR^d-A-H. Progroups including linkages capable of metabolizing in vivo to yield such an intermediate group are well-known, and include, by way of example and not limitation, ethers, thioethers, silylethers, silylthioethers, esters, thioesters, carbonates, thiocarbonates, carbamates, thiocarbamates, ureas, thioureas, carboxamides, etc. In some instances, a "precursor" group that is oxidized by oxidative enzymes such as, for example, cytochrome P450 of the liver, to a metabolizable group, can be selected.

The identity of the R^3 group can also be selected so as to impart the prodrug with desirable characteristics. For example, lipophilic groups can be used to decrease water solubility and hydrophilic groups can be used to increase water solubility. In this way, prodrugs specifically tailored for selected modes of administration can be obtained. The R^3 group can also be designed to impart the prodrug with other properties, such as, for example, improved passive intestinal absorption, improved transport-mediated intestinal absorption, protection against fast metabolism (slow-release prodrugs), tissue-selective delivery, passive enrichment in target tissues, targeting-specific transporters, etc. Groups capable of imparting prodrugs with these characteristics are well-known, and are described, for example, in Ettmayer et al., 2004, J. Med. Chem. 47(10:2393-2404), the disclosure of which is incorporated by reference. All of the various groups described in these references can be utilized in the prodrugs described herein.

In some embodiments, R^3 is selected from —R^f, —$C(O)R^f$, —$C(O)NR^fR^f$ and —$SiR^fR^fR^f$, where the R^f groups are selected so as to impart the prodrugs with desired bioavailability, cleavage and/or targeting properties. In a specific embodiment, the R^f groups are selected to impart the prodrug with higher water-solubility than the underlying active 2,4-pyrimidinediamine drug. Thus, in some embodiments, the R^f groups are selected such that they, taken together with the heteroatom or group to which they are bonded, are hydrophilic in character. Such hydrophilic groups can be charged or uncharged, as is well-known in the art. As specific examples, the R^f groups may be selected from hydrogen, optionally substituted lower alkyl, optionally substituted lower heteroalkyl, optionally substituted lower cycloalkyl, optionally substituted lower heterocycloalkyl, optionally substituted (C6-C10) aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted (C7-C18) arylalkyl and optionally substituted 6-18 membered heteroarylalkyl. The nature of any present substituents can vary widely, as is known in the art. In some embodiments any present substituents are, independently of one another, selected from R^b, defined above.

In a specific embodiment, the progroups on the prodrugs of formula (I) and/or (Ia) are of the formula —CR^dR^d-A-R^3, where R^3 is selected from —$(CH_2)_i$—R^b, —$C(O)R^a$, —$C(O)$—$(CH_2)_i$—R^b, —$C(O)O$—R^a and —$C(O)O$—$(CH_2)_i$—R^b, where X, R^a, R^b and R^d are as previously defined, and i is an integer ranging from 0 to 6. Specific, non-limiting, examples of exemplary water-solubility increasing progroups include by the way of example and not limitation, hydrophilic groups such as alkyl, arylk, arylalkyl, or cycloheteroalkyl groups substituted with one or more of an amine, alcohol, a carboxylic acid, a phosphorous acid, a sulfoxide, a sugar, an amino acid, a thiol, a polyol, a ether, a thioether and a quaternary amine salt.

One important class of progroups includes progroups that contain a phosphate group, for example, phosphate-containing progroups of the formula —$(R^dR^d)_y$—O—$P(O)(OH)_2$, where R^d is as defined above and y is an integer ranging from 1 to 3, typically 1 or 2. In a specific embodiment, each R^d is, independently of the others, selected from hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted (C6-C14) aryl and substituted or unsubstituted (C7-C20) arylalkyl.

While not intending to be bound by any theory of operation, it is believed that such phosphate-containing progroups R^P act as substrates for both alkaline and acid phosphatase enzymes, leading to their removal from the prodrugs under physiological conditions of use. As alkaline phosphatases are abundant in the digestive tract of humans, phosphate-containing progroups R^P that can be cleaved in the presence of alkaline phosphatases are particularly suitable for formulating phosphate-containing prodrugs intended for oral administration. Specific examples of phosphate-containing progroups R^P suitable for use in prodrugs intended for oral administration include, but are not limited to, groups of the formula —$(R^dR^d)_y$—O—$P(O)(OH)_2$ in which each R^d is, independently of the others, selected from hydrogen and unsubstituted lower alkanyl. Exemplary embodiments of such phosphate-containing progroups include, but are not limited to, —CH_2—O—$P(O)(OH)_2$ and —CH_2CH_2—O—$P(O)(OH)_2$.

Although phosphate-containing prodrugs suitable for oral administration are of interest, skilled artisans will appreciate that prodrugs including phosphate-containing progroups R^P can be administered via other routes of administration, as phosphatases are distributed throughout the body. For example, exemplary prodrug Compound 4 has been found to metabolize to the active drug Compound 1 in in vitro experiments carried out with rat plasma, as well as with rat hepatic and intestinal microsomal preparations, indicating that phosphatases are also present in plasma. Thus, the only requirement is that the particular phosphate-containing progroup R^P selected should be removable under the conditions of intended use.

While not intending to be bound by any theory of operation, it is believed that when y is 1, phosphate-containing prodrugs, such as those according to structural formula (Ia), are metabolized to the active 2,4-pyrimidinediamine compound via the corresponding hydroxymethylamine. This metabolism is illustrated in FIG. **1**A. Referring to FIG. **1**A, removal of phosphoric acid from phosphate prodrug 16 via enzymatic hydrolysis yields the corresponding hydroxymethylamine 18, which undergoes hydrolysis in vivo to yield formaldehyde and active 2,4-pyrimidinediamine compound 10.

Referring to FIG. **1**B, when y is 2, it is believed that in vivo hydrolysis of phosphate prodrug 26 yields active 2,4-pyrimidinediamine 10 and enol phosphate, which then hydrolyses in vivo to acetaldehyde and phosphoric acid.

Referring again to FIG. **1**A, skilled artisan will appreciate that while hydroxymethylamine 18 metabolizes under physiological conditions to yield active 2,4-pyrimidinediamine compound 10, it is stable at pH 7 and can therefore be prepared and administered as a hydroxyalkyl-containing prodrug of active compound 10. Thus, in some embodiments of

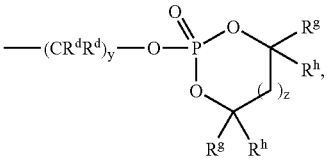
the prodrugs of structural formula (I), R^p is a hydroxyalkyl-containing progroup of the formula —CR^dR^d—OH, where R^d is as previously defined. In a specific exemplary embodiment, R^p is —CH_2OH.

Still referring again to FIG. **1**A, skilled artisans will also appreciate that phosphate prodrugs can be generated by in vivo hydrolysis of phosphate ester prodrugs, such as phosphate ester prodrugs 20 and/or by in vivo oxidation of phosphite prodrugs, such as phosphite prodrugs 24. Such phosphate ester and phosphite prodrugs can in turn be generated by either in vivo oxidation or hydrolysis of phosphite ester prodrugs such as phosphite ester prodrugs 22. The corresponding phosphate ester, phosphite and phosphite ester prodrugs of phosphate prodrug 26 are illustrated in FIG. **1**B as compounds 30, 34 and 32, respectively. Thus, as will be appreciated by skilled artisans, prodrugs that include precursors of phosphates that can metabolize into phosphate groups in vivo are also included in the present invention.

In some embodiments of such prodrugs, the phosphorous-containing progroup R^p comprises a phosphite group. A specific exemplary embodiment of such phosphite-containing prodrugs includes prodrug compounds in which the progroup R^p is of the formula —$(CR^dR^d)_y$—O—P(OH)(OH), where R^d and y are as previously defined.

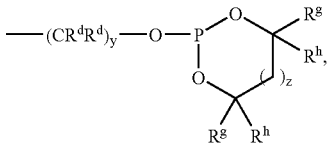
In other embodiments of such prodrugs, the phosphorous-containing progroup R^p comprises an acyclic phosphate ester or phosphite ester group. Specific exemplary embodiments of such acyclic phosphate ester and phosphite ester prodrugs include progroups R^p of the formula —$(CR^dR^d)_y$—O—P(O)(OH)(OR^e), —$(CR^dR^d)_y$—O—P(O)(OR^e)$_2$, —$(CR^dR^d)_y$—O—P(OH)(OR^e) and —$(CR^dR^d)_y$—O—P(OR^e)$_2$, where R^e is selected from substituted or unsubstituted lower alkyl, substituted or unsubstituted (C6-C14) aryl (e.g., phenyl, naphthyl, 4-lower alkoxyphenyl, 4-methoxyphenyl), substituted or unsubstituted (C7-C20) arylalkyl (e.g., benzyl, 1-phenylethan-1-yl, 2-phenylethan-1-yl), —$(CR^dR^d)_y$—OR^f, —$(CR^dR^d)_y$—O—C(O)R^f, —$(CR^dR^d)_y$—O—C(O)OR^f, —$(CR^dR^d)_y$—S—C(O)R^f, —$(CR^dR^d)_y$—S—C(O)OR^f, —$(CR^dR^d)_y$—NH—C(O)R^f, —$(CR^dR^d)_y$—NH—C(O)OR^f and —$Si(R^d)_3$, wherein each R^f is, independently of the others, selected from hydrogen, unsubstituted or substituted lower alkyl, substituted or unsubstituted (C6-C14) aryl, and substituted or unsubstituted (C7-C20) arylalkyl, and R^d and y are as previously defined.

In still other embodiments, phosphorous-containing prodrugs that include phosphate precursors are prodrugs in which the phosphorous-containing progroup R^p comprises a cyclic phosphate ester of the formula



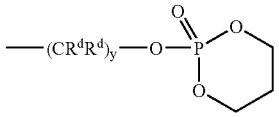
where each R^g is, independently of the others, selected from hydrogen and lower alkyl; each R^h is, independently of the others, selected from hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower cycloheteroalkyl, substituted or unsubstituted (C6-C14) aryl, substituted or unsubstituted (C7-C20) arylalkyl and substituted or unsubstituted 5-14 membered heteroaryl; z is an integer ranging from 0 to 2; and R^d and y are as previously defined.

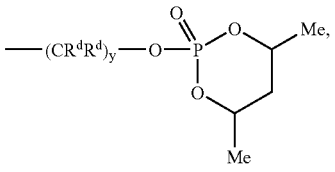
In still other embodiments, phosphorous-containing prodrugs that include phosphate precursors are prodrugs in which the phosphorous-containing progroup R^p comprises a cyclic phosphite ester of the formula

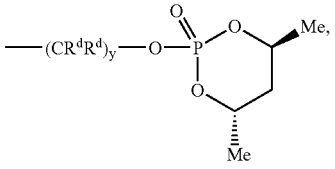


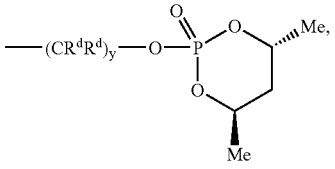
where R^g, R^h, R^d, y and z are as previously defined.

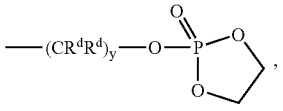
In some embodiments, the substituents R^h on such cyclic phosphate ester and phosphite ester prodrugs are selected such that the progroup is metabolized in vitro by esterase enzymes. Specific examples of such phosphate ester and phosphite ester progroups include those in which each R^h is, independently of the others, selected from hydrogen, lower alkyl, methyl, ethyl and propyl. In some embodiments, such progroups are selected from

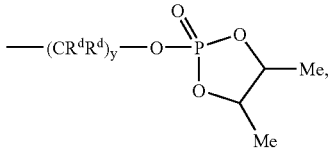


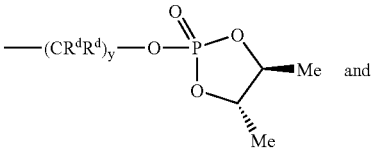












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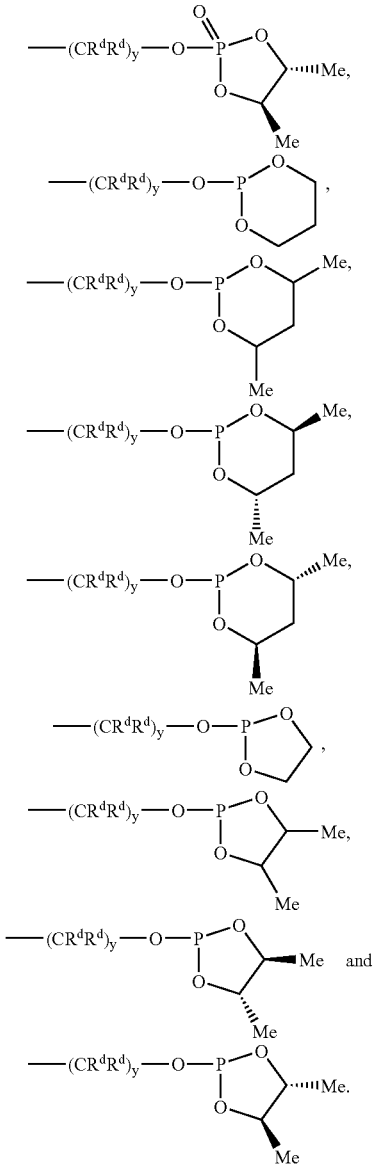


Many of these phosphate esters and phosphite esters are acid label and, when administered orally, metabolize to the corresponding phosphates and phosphites under the acidic conditions of the stomach and/or gut.

Thus, in the phosphorous-containing prodrugs described herein, the identity of the particular phosphorous-containing progroups R^p employed can be selected to tailor the prodrugs for particular modes of delivery, etc.

The suitability of any particular progroup R^p for a desired mode of administration can be confirmed in biochemical assays. For example, if a prodrug is to be administered by injection into a particular tissue or organ, and the identities of the various phosphatases expressed in the tissue or organ are known, the particular prodrug can be tested for metabolism in biochemical assays with the isolated phosphatase(s). Alternatively, the particular prodrug can be tested for metabolism to the active 2,4-pyrimidinediamine compound with tissue and/or organ extracts. Using tissue and/or organ extracts can be of particular convenience when the identity(ies) of the phosphatases expressed in the target tissues or organs are unknown, or in instances when the isolated phosphatases are not conveniently available. Skilled artisans will be able to readily select progroups R^p having metabolic properties (such as kinetics) suitable for particular applications using such in vitro tests. Of course, specific prodrugs could also be tested for suitable metabolism in in vitro animal models.

In some embodiments, the prodrugs are prodrugs according to structural formula (I) or (Ia) that have one or more features selected from:

(i) R^5 is fluoro;

(ii) R^2 is a phenyl optionally substituted with one or more of the same or different R^8 groups;

(iii) R^2 is 3,4,5-tri(loweralkoxy)phenyl;

(iv) R^2 is 3,4,5-trimethoxyphenyl;

(v) Y or Y^1 is O; Z^1 is CH, Z^2 is N; R^{17} and R^{18} are each methyl; and R^{19} and R^{20} are taken together to form an oxogroup; and

(vi) R^p is a hydroxyalkyl-containing progroup of the formula —CH_2OH, or a phosphate-containing progroup of the formula —$(CR^dR^d)_y$—O—$P(O)(OH)_2$, or a phosphate ester, phosphite or phosphite ester analog thereof, wherein y is 1 or 2 and each R^d is, independently of the others, selected from hydrogen and unsubstituted lower alkyl, or

(vii) R^p is selected from —CH_2OH, CH_2—SH, —CH_2—NH_2, —CH_2—NHR^{50}, —CH_2—$N(R^{50})_2$, —CH_2-A-R^f, —CH_2-A-C(O)R^f, —CH_2-A-C(O)OR^f and —CH_2-A-C(O)NR^fR^f, where A, R^{50} and R^f are as previously defined.

In some embodiments, the prodrugs of structural formulae (I) and (Ia) have two or three of the above-delineated features. In one specific embodiment, the prodrugs have features (i), (iii) and (v). In another specific embodiment, the prodrugs have features (i), (iv) and (v). In still another specific embodiment, the prodrugs have features (i), (iii), (v) and (vi) or (vii). In still another specific embodiment, the prodrugs have features (i), (iv), (v) and (vi) or (vii). In still another specific embodiment, R^p is a phosphate-containing progroup of the formula —$(CR^dR^d)_y$—O—$P(O)(OH)_2$.

In all of the compounds described herein that include substituent alternatives that may be substituted, such as, for example, some of the substituent alternatives delineated for R^d, R^e, R^f, R^g, R^h, R^i and R^j, the substitutions are typically, independently of one another, selected from amongst the R^b groups described in connection with structural formula (I). In a specific embodiment, any present substitutions are, independently of one another, selected from hydroxyl, lower alkoxy, (C6-C14) aryloxy, lower alkoxyalkyl, methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl and halogen.

Those of skill in the art will appreciate that many of the prodrugs described herein, as well as the various prodrug species specifically described and/or illustrated herein, may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism and/or optical isomerism. For example, the prodrugs may include one or more chiral centers and/or double bonds and as a consequence may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers and diasteromers and mixtures thereof, such as racemic mixtures. As another example, the prodrugs may exist in several tautomeric forms, including the enol form, the keto form and mixtures thereof. As the various compound names, formulae and drawings within the specification and claims can represent only one of the possible tautomeric, conformational isomeric, optical isomeric or geometric isomeric forms, it should be understood that the invention encompasses any tautomeric, conformational isomeric,

optical isomeric and/or geometric isomeric forms of the prodrugs having one or more of the utilities described herein, as well as mixtures of these various different isomeric forms. In cases of limited rotation around the 2,4-pryimidinediamine moiety, atrop isomers are also possible and are also specifically included in the compounds of the invention.

Moreover, skilled artisans will appreciate that when lists of alternative substituents include members which, owing to valency requirements or other reasons, cannot be used to substitute a particular group, the list is intended to be read in context to include those members of the list that are suitable for substituting the particular group. For example, skilled artisans will appreciate that while all of the listed alternatives for R^b can be used to substitute an alkyl group, certain of the alternatives, such as =O, cannot be used to substitute a phenyl group. It is to be understood that only possible combinations of substituent-group pairs are intended.

The prodrugs described herein may be identified by either their chemical structure or their chemical name. When the chemical structure and the chemical name conflict, the chemical structure is determinative of the identity of the specific prodrug.

Depending upon the nature of the various substituents, the prodrugs described herein may be in the form of salts. Such salts include salts suitable for pharmaceutical uses ("pharmaceutically-acceptable salts"), salts suitable for veterinary uses, etc. Such salts may be derived from acids or bases, as is well-known in the art.

In one embodiment, the salt is a pharmaceutically acceptable salt. Generally, pharmaceutically acceptable salts are those salts that retain substantially one or more of the desired pharmacological activities of the parent compound and which are suitable for administration to humans. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids or organic acids. Inorganic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, hydrohalide acids (e.g., hydrochloric acid, hydrobromic acid, hydriodic, etc.), sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, oxalic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, palmitic acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, alkylsulfonic acids (e.g., methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, etc.), arylsulfonic acids (e.g., benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, etc.), 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

Pharmaceutically acceptable salts also include salts formed when an acidic proton present in the parent compound is either replaced by a metal ion (e.g., an alkali metal ion, an alkaline earth metal ion or an aluminum ion) or coordinates with an organic base (e.g., ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, piperidine, dimethylamine, diethylamine, etc.).

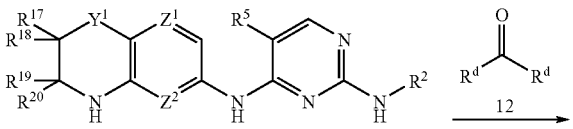
The prodrugs described herein, as well as the salts thereof, may also be in the form of hydrates, solvates and N-oxides, as are well-known in the art. Unless specifically indicated otherwise, the expression "prodrug" is intended to encompass such salts, hydrates, solvates and/or N-oxides. Specific exemplary salts include, but are not limited to, mono- and di-sodium salts, mono- and di-potassium salts, mono- and di-lithium salts, mono- and di-alkylamino salts, mono-magnesium salts, mono-calcium salts and ammonium salts.

6.3 Methods of Synthesis

The prodrugs described herein, as well as intermediates therefor, may be synthesized via a variety of different synthetic routes using commercially available starting materials and/or starting materials prepared by conventional synthetic methods. Suitable exemplary methods that may be routinely used and/or adapted to synthesize active 2,4-pyrimidinediamine compounds can be found in U.S. Pat. No. 5,958,935, U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Ser. No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893), the disclosures of which are incorporated herein by reference. These active 2,4-pyrimidinediamine compounds can be used as starting materials to synthesize the prodrugs. Specific examples describing the synthesis of phosphate prodrug Compound 4, as well as a synthetic intermediate therefor, are provided in the Examples section. All of the prodrugs described herein may be synthesized by routine adaptation of this method.

For example, some embodiments of prodrugs according to structural formula (I) and/or (Ia) can be prepared by reacting the corresponding active 2,4-pyrimidinediamine (i.e., compounds according to structural formulae (I) and/or (Ia) in which each R^p is hydrogen) with an aldehyde or a ketone to give an α-hydroxymethyl amine, which can then be reacted with an electrophile to yield a prodrug. An exemplary synthesis of this type is illustrated in Scheme (I), below:

Scheme (I)



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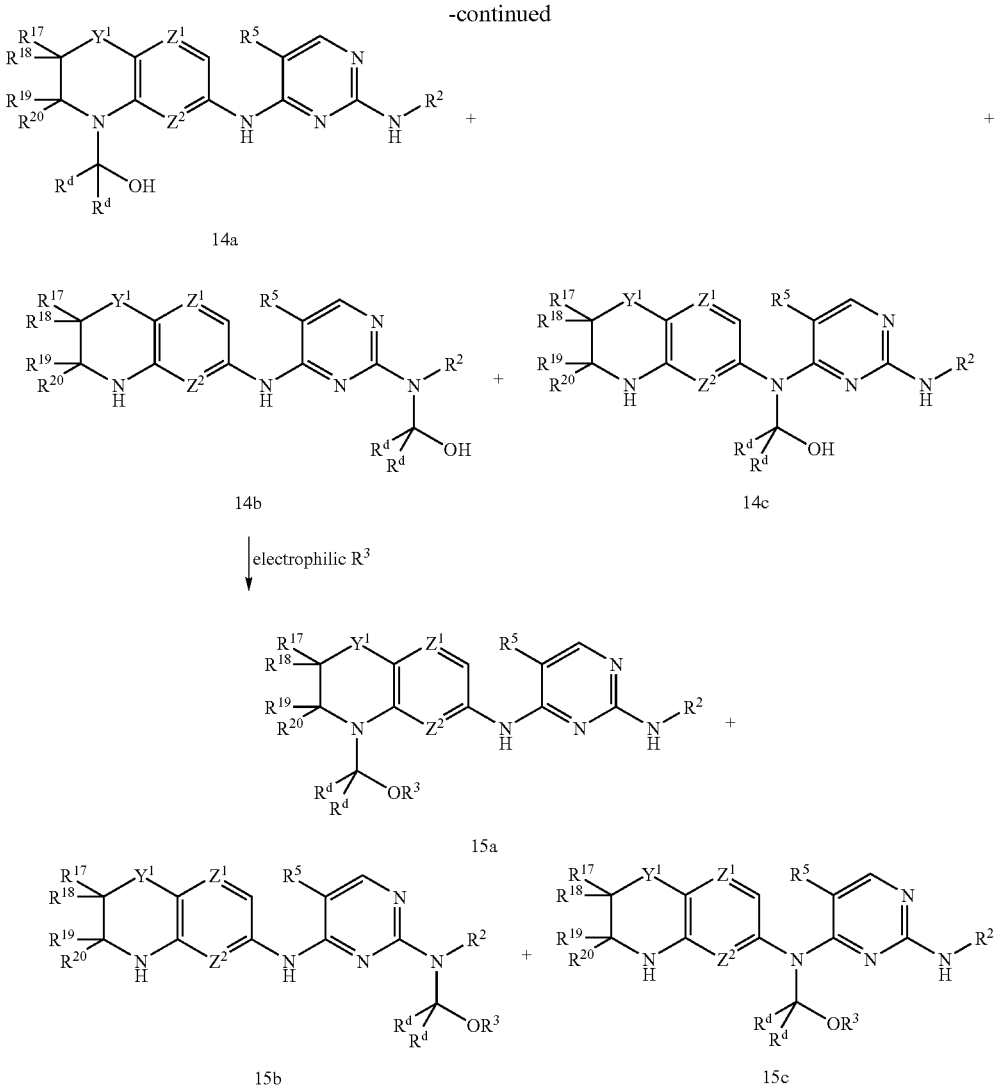


14a

14b

14c

electrophilic R^3

15a

15b

15c

In Scheme (I), Y^1, Z^1, Z^2, R^2, R^5, R^{17}, R^{18}, R^{19} and R^{20} are as defined for structural formula (I) or (Ia). R^3 and R^d are as defined in the text, supra. According to Scheme (I), active 2,4-pyrimidinediamine **10** is reacted with ketone **12** to yield a mixture of four products: unreacted starting material **10** (not illustrated) and compounds **14***a*, **14***b* and **14***c*. At this stage, the products can be isolated from one another using standard chromatographic techniques. Reaction with electropholic R^3 yields prodrugs **15***a*, **15***b* and **15***c*.

As illustrated above, α-hydroxymethylamines **14***a*, **14***b* and **14***c* can be converted into a variety of different types of prodrugs **15***a*, **15***b* and **15***c*. For example, the α-hydroxymethylamines can be reacted with an alcohol in the presence of a strong acid catalyst, or a carbon-bearing halide (e.g., CH_3Br), to yield the corresponding ether derivatives (e.g., compounds in which R^3 is R^f, where R^f is as previously defined).

Reacting α-hydroxymethylamines **14***a*, **14***b* and **14***c* with a carboxylic acid in the presence of a strong acid catalyst or a carboxylic acid anhydride or a carboxylic acid halide (e.g. with an appropriate acid scavenger) yields the corresponding ester derivatives (e.g., compounds in which R^3 is —C(O)R^f, where R^f is as defined above).

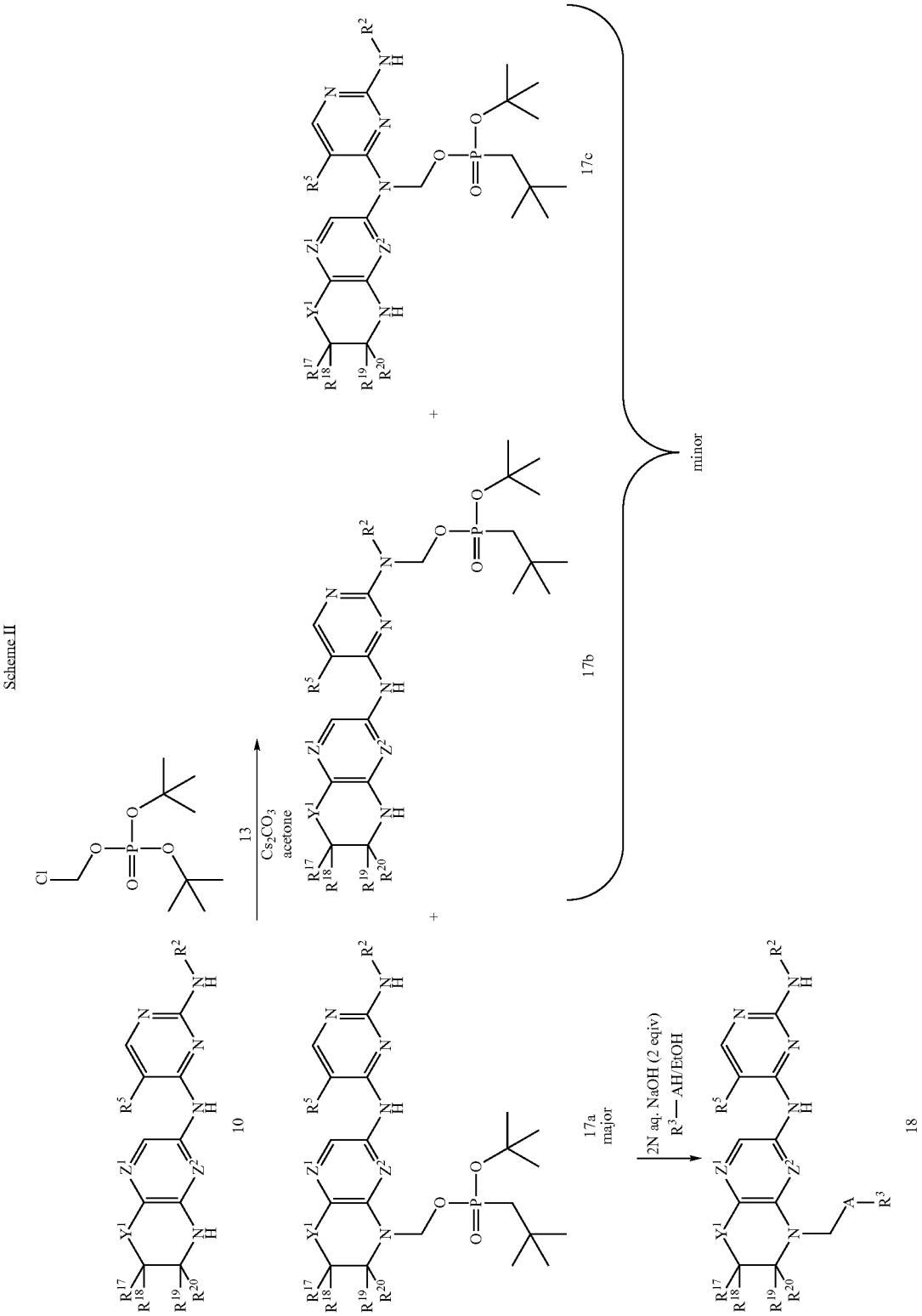
Reaction of α-hydroxymethylamines **14***a*, **14***b*and **14***c* with a haloformate ester (e.g., Cl—C(O)OCH_3) yields the corresponding carbonate derivatives (e.g., compounds in which R^3 is —C(O)OR^f, where R^f is as previously defined).

Reaction of α-hydroxymethylamines **14***a*, **14***b* and 14*c* with a haloformamide (e.g., Cl—C(O)$N(CH_3)_2$) yields the corresponding carbamate or urethane derivatives (e.g., compounds in which $R^3$is —C(O)NR^fR^f, where R^f is as previously defined).

As will be recognized by skilled artisans, other hydroxyl protecting groups could also be used, including, for example, the various different hydroxyl protecting groups described in Green & Wuts, "*Protective Groups in Organic Chemistry,*" 2d Edition, John Wiley & Sons, New York, pp. 10-142, the disclosure of which is incorporated herein by reference.

Alternatively, prodrugs according to structural formulae (I) and (Ia) can be synthesized by nucleophilic substitution of the corresponding phosphate esters. An example of this synthetic route is illustrated in Scheme (II), below:

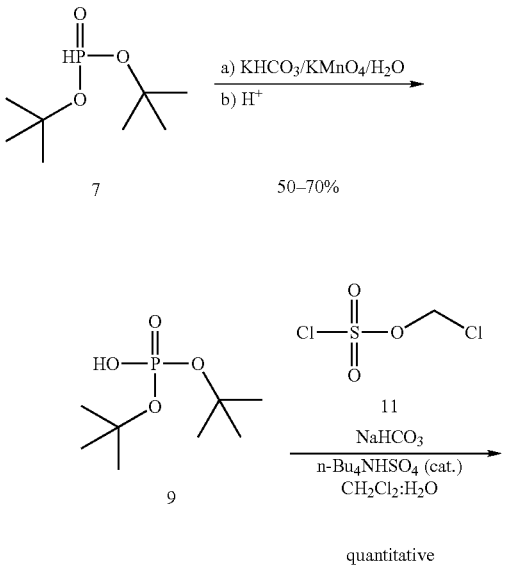
Scheme II


Cl
13
Cs_2CO_3
acetone
10
17a
major
17b
17c
minor
2N aq. NaOH (2 eqiv)
R^3— AH/EtOH
18

According to Scheme (II), active 2,4-pyrimidinediamine **10** is reacted with di-tert-butyl chloromethylphosphate **13** in the presence of cesium carbonate to yield a mixture of four products: unreacted starting material **10** (not illustrated) and phosphate esters **17***a*, **17***b* and **17***c*, which are themselves prodrugs as described herein. When R^2 is 3,4,5-trimethoxyphenyl phosphate ester **17***a* is the major product. Reaction of this phosphate ester **17***a* with R^3-AH (where A is O, S, or NR^{50}), yields prodrug **19**. The minor phosphate esters **17***b* and **17***c* can be similarly reacted to yield the corresponding prodrugs.

Di-tert-butyl chloromethyl phosphate **13** can be prepared from di-tert-butyl phosphate as illustrated in Scheme (III), below:

Scheme (III)



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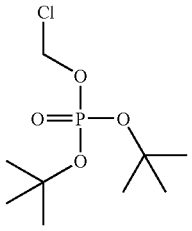


13

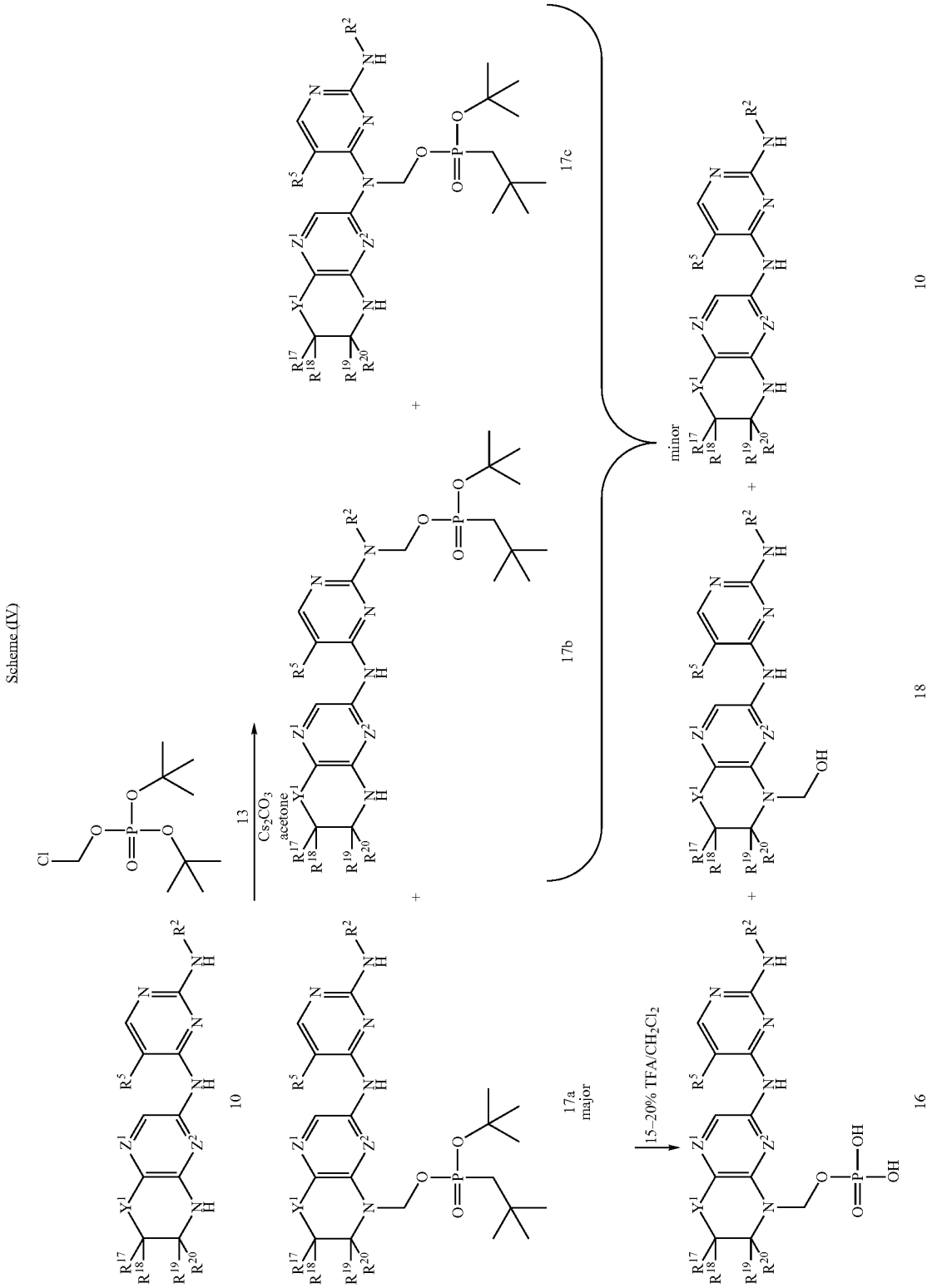
According to Scheme (III), di-tert-butyl phosphate **9** is obtained from the corresponding di-tert-butyl phosphite **7** as described in Krise et al., 1999, J. Med. Chem. 42:3094-3100. Reaction of phosphate **9** with chloromethyl chlorosulfate **11** (available from Synergetica, Inc., Sicklerville, N.J. 08081) as described in Mantyla et al., 2002, Tet. Lett. 43:3793-3794 yields di-tert-butyl chloromethyl phosphate **13**, which can be used in Scheme (II), above, crude without purification.

Although the Schemes illustrated above depict the synthesis of prodrugs that include a single progroup, prodrugs having a plurality of progroups could be obtained by adjusting the number of equivalents of reagent **12** or **13** used.

As another alternative to Scheme (I), hydroxymethylamine **14***a* can be prepared in a two-step process by first reacting active 2,4-pyrimidinediamine **10** with a bis functional electrophile, such as, for example, chloro-iodomethane (I—CH_2Cl), to yield a chloro-methyl intermediate, which can then be hydroxylated by reaction with basic hydroxide or reacted with various nucleophilic reagents such as alkoxides, amines or sulfide to make R^p. Specific conditions for carrying out reactions of this type that can be used to synthesize the prodrugs described herein, for example, in Bansal et al., 1981, J. Pharm. Sci. 70(8):850-854 and Bansal et al., 1981, J. Pharm. Sci. 70(8):855-857, the disclosures of which are incorporated herein by reference.

An exemplary synthetic route that can be used to synthesize an exemplary phosphate prodrug **16** according to structural formula (Ia) is illustrated in Scheme (IV), below. This method may be routinely adapted to synthesize the full range of phosphate prodrugs described herein.

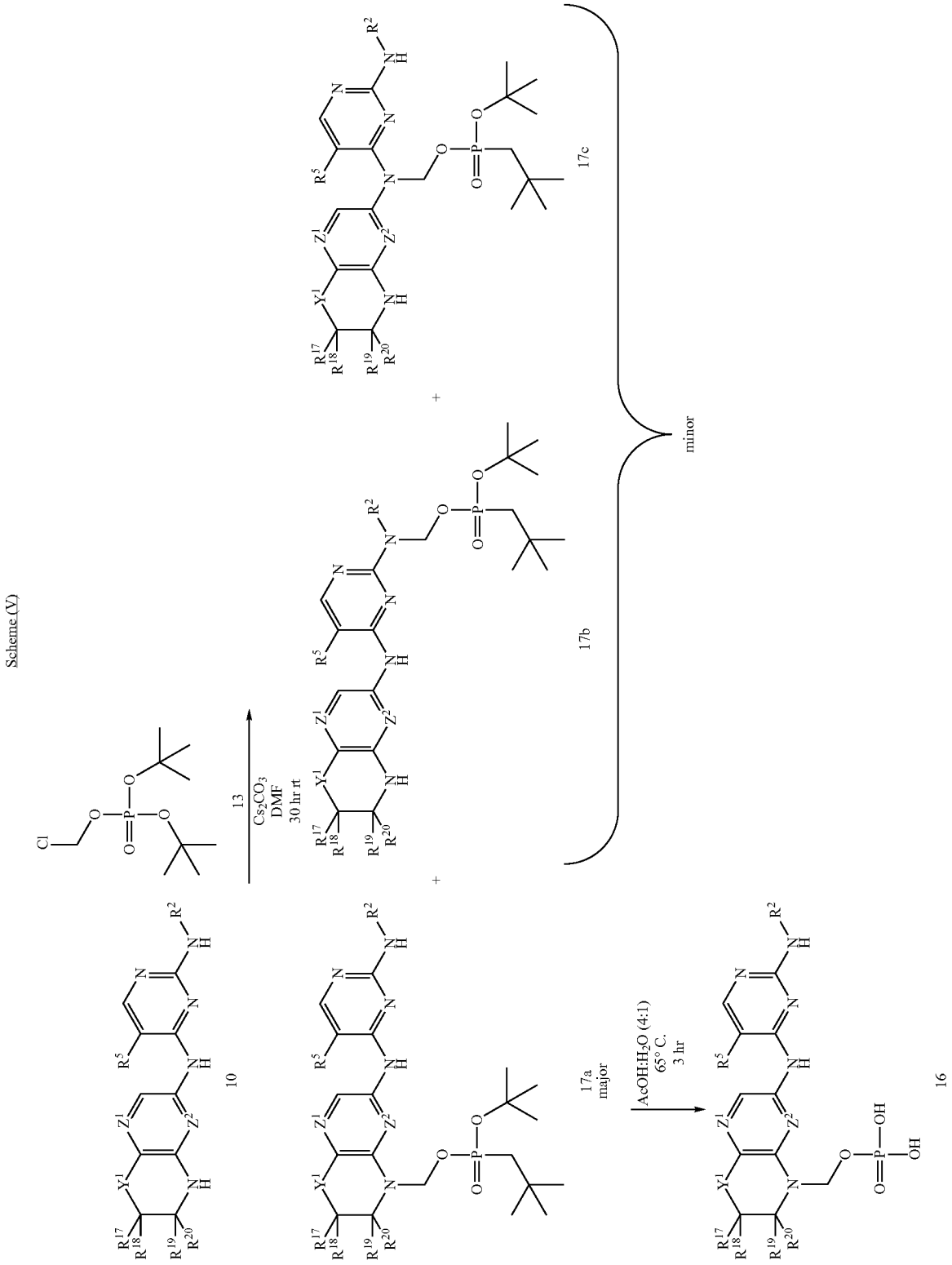
Scheme (IV)


Cl
13
Cs_2CO_3
acetone
10
17a
major
17b
17c
minor
15–20% TFA/CH_2Cl_2
16
18
10

In Scheme (IV), Y^1, Z^1, Z^2, R^2, R^5, R^{17}, R^{18}, R^{19} and R^{20} are as defined for structural formula (I) or (Ia). According to Scheme (IV), active 2,4-pyrimidinediamine **10** is reacted with di-tert-butyl chloromethylphosphate **13** in the presence of cesium carbonate to yield a mixture of four products: unreacted starting material **10** (not illustrated) and compounds **17***a*, **17***b* and **17***c*. When R^2 is 3,4,5-trimethyoxyphenyl, compound **17***a* is the major product. At this stage, the major product can be isolated from the minor products using standard chromatographic techniques. Removal of the tert-butyl groups yields a mixture of desired product **16** and impurities **18** and **10**. The desired product **16** can be isolated using standard techniques.

An alternative method of obtaining phosphate prodrug **16** is illustrated in Scheme (V); below.

Scheme (V)


Cl
13
Cs_2CO_3
DMF
30 hr rt
10
17a
major
17b
17c
minor
$AcOH:H_2O$ (4:1)
65° C.
3 hr
16

According to Scheme (V), the reaction of active 2,4-pyrimidinediamine **10** again yields a mixture of four products: unreacted pyrimidinediamine **10** (not illustrated) major product **17***a* and minor products **17***b* and **17***c*. Major product **17***a* can be isolated via crystallization (see the Examples section for suitable conditions), dissolved in a mixture of acetic acid and water (4:1 AcOH:H_2O) and heated to 65° C. for approximately 3 hr to yield phosphate prodrug 16 as the major product.

Although Schemes (IV) and (V) illustrate the synthesis of a phosphate prodrug in which the phosphate progroup is —CH_2—O—P(O)$(OH)_2$, skilled artisans will appreciate that phosphate prodrugs including other phosphate progroups could be readily obtained according to the same methods by using the appropriate reagent **13**. Phosphate ester prodrugs, phosphite prodrugs and phosphite ester prodrugs can also be synthesized via routine adaptation of the methods using the appropriate phosphate ester, phosphite and phosphite ester halides **13**. Exemplary methods for synthesizing cyclic phosphate ester prodrugs, which can be used as prodrugs in the various methods described herein, or converted into phosphate prodrugs, are illustrated in FIG. **3**. Moreover, while Schemes (I) and (III) depict compound **16** as being the desired product, prodrugs having progroups at other positions within the prodrug molecule could be readily obtained by isolating, for example minor product **17***a* or **17***b* and/or by adjusting the number of equivalents of reagent **13** used.

Referring to FIG. **3**, diols **21** are converted to the corresponding cyclic phosphates **23** using literature procedures as depicted. Cyclic phosphates **23** are converted to the corresponding chloromethyl phosphate esters **25** in any of the three ways depicted. Compound **1** is converted to cyclic phosphate ester derivatives **27**, **29**, and **31**, via addition of **25** under conditions as previously described for the synthesis of compounds **17***a-c*. Cyclic phosphate ester derivatives **27**, **29**, and **31**, are converted to the corresponding phosphate derivatives via treatment under acidic conditions as described for the synthesis of compound **16**, or via hydrogenation using, for example, palladium catalyst.

Skilled artisans will recognize that in some instances, the active 2,4-pyrimidinediamine compounds used as starting materials may include functional groups that require protection during synthesis. The exact identity of any protecting group(s) used will depend upon the identity of the functional group being protected, and will be apparent to these of skill in the art. Guidance for selecting appropriate protecting groups, as well as synthetic strategies for their attachment and removal, may be found, for example, in Greene & Wuts, Protective Groups in Organic Synthesis, 3d Edition, John Wiley & Sons, Inc., New York (1999) and the references cited therein (hereinafter "Greene & Wuts").

6.4 Inhibition of Fc Receptor Signal Cascades

Many of the prodrugs described herein, and in particular the prodrugs according to structural formulae (I) and (Ia), metabolize to active 2,4-pyrimidinediamine compounds that inhibit Fc receptor signaling cascades that lead to, among other things, degranulation of cells.

As a specific example, these active compounds inhibit the FcεRI and/or FcγRI signal cascades that lead to degranulation of immune cells such as neutrophil, eosinophil, mast and/or basophil cells. Both mast and basophil cells play a central role in allergen-induced disorders, including, for example, allergic rhinitis and asthma. Upon exposure allergens, which may be, among other things, pollen or parasites, allergen-specific IgE antibodies are synthesized by B-cells activated by IL-4 (or IL-13) and other messengers to switch to IgE class specific antibody synthesis. These allergen-specific IgEs bind to the high affinity FcεRI. Upon binding of antigen, the FcεR1-bound IgEs are cross-linked and the IgE receptor signal transduction pathway is activated, which leads to degranulation of the cells and consequent release and/or synthesis of a host of chemical mediators, including histamine, proteases (e.g., tryptase and chymase), lipid mediators such as leukotrienes (e.g., LTC4), platelet-activating factor (PAF) and prostaglandins (e.g., PGD2) and a series of cytokines, including TNF-α, IL-4, IL-13, IL-5, IL-6, IL-8, GMCSF, VEGF and TGF-β. The release and/or synthesis of these mediators from mast and/or basophil cells accounts for the early and late stage responses induced by allergens, and is directly linked to downstream events that lead to a sustained inflammatory state.

The molecular events in the FcεRI signal transduction pathway that lead to release of preformed mediators via degranulation and release and/or synthesis of other chemical mediators are well-known. The $FcεR^p$ is a heterotetrameric receptor composed of an IgE-binding alpha-subunit, a beta subunit, and two gamma subunits (gamma homodimer). Cross-linking of FcεRI-bound IgE by multivalent binding agents (including, for example IgE-specific allergens or anti-IgE antibodies or fragments) induces the rapid association and activation of the Src-related kinase Lyn. Lyn phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMS) on the intracellular beta and gamma subunits, which leads to the recruitment of additional Lyn to the beta subunit and Syk kinase to the gamma homodimer. These receptor-associated kinases, which are activated by intra- and intermolecular phosphorylation, phosphorylate other components of the pathway, such as the Btk kinase, LAT, and phospholipase C-gamma PLC-gamma). Activated PLC-gamma initiates pathways that lead to protein kinase C activation and Ca^{2+} mobilization, both of which are required for degranulation. FcεR1 cross-linking also activates the three major classes of mitogen activated protein (MAP) kinases, i.e. ERK1/2, JNK1/2, and p38. Activation of these pathways is important in the transcriptional regulation of proinflammatory mediators, such as TNF-α and IL-6, as well as the lipid mediator leukotriene C4 (LTC4).

The FcγRI signaling cascade is believed to share some common elements with the FceRI signaling cascade. Importantly, like FcεRI, the FcγRI includes a gamma homodimer that is phosphorylated and recruits Syk, and like FcεRI, activation of the FcγRI signaling cascade leads to, among other things, degranulation. Other Fc receptors that share the gamma homodimer, and which can be regulated by the active 2,4-pyrimidinediamine compounds include, but are not limited to, FcαRI and FcγRIII.

In vitro and cellular assays suitable for confirming the activity of a particular 2,4-pyrimidinediamine compound are described in detail in U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Ser. No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO02004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893).

The ability of a particular prodrug to metabolize to an active 2,4-pyrimidinediamine compound under the desired conditions of use can be confirmed in in vitro and/or in vivo assays, as previously described.

6.5 Uses and Compositions

As previously discussed, the prodrugs described herein, such as the prodrugs according to structural formulae (I) and (Ia) metabolize when administered to animals and humans into active compounds that inhibit Fc receptor signaling cascades, especially those Fc receptors including a gamma homodimer, such as the FcεRI and/or FcγRI signaling cascades, that lead to, among other things, the release and/or synthesis of chemical mediators from cells, either via degranulation or other processes. As also discussed, the active compounds are also potent inhibitors of Syk kinase. As a consequence of these activities, prodrugs of these active compounds may be used in a variety of in vitro, in vivo and ex vivo contexts to regulate or inhibit Syk kinase, signaling cascades in which Syk kinase plays a role, Fc receptor signaling cascades, and the biological responses effected by such signaling cascades. For example, in one embodiment, the prodrugs may be used to inhibit Syk kinase, either in vitro or in vivo, in virtually any cell type expressing Syk kinase. They may also be used to regulate signal transduction cascades in which Syk kinase plays a role. Such Syk-dependent signal transduction cascades include, but are not limited to, the FcεRI, FcγRI, FcγRIII, BCR and integrin signal transduction cascades. The prodrugs may also be used in vitro or in vivo to regulate, and in particular inhibit, cellular or biological responses effected by such Syk-dependent signal transduction cascades. Such cellular or biological responses include, but are not limited to, respiratory burst, cellular adhesion, cellular degranulation, cell spreading, cell migration, cell aggregation, phagocytosis, cytokine synthesis and release, cell maturation and Ca^{2+} flux. Importantly, the prodrugs may be used to inhibit Syk kinase in vivo as a therapeutic approach towards the treatment or prevention of diseases mediated, either wholly or in part, by a Syk kinase activity. Non-limiting examples of Syk kinase mediated diseases that may be treated or prevented with the prodrugs are those discussed in more detail, below.

In another embodiment, the prodrugs may be used to regulate or inhibit the Fc receptor signaling cascades and/or FcεRI- and/or FcγRI-mediated degranulation as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by and/or associated with the release or synthesis of chemical mediators of such Fc receptor signaling cascades or degranulation. Such treatments may be administered to animals in veterinary contexts or to humans. Diseases that are characterized by, caused by or associated with such mediator release, synthesis or degranulation, and that can therefore be treated or prevented with the active compounds include, by way of example and not limitation, atopy or anaphylactic hypersensitivity or allergic reactions, allergies (e.g., allergic conjunctivitis, allergic rhinitis, atopic asthma, atopic dermatitis and food allergies), low grade scarring (e.g., of scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction), diseases associated with tissue destruction (e.g., of COPD, cardiobronchitis and post myocardial infarction), diseases associated with tissue inflammation (e.g., irritable bowel syndrome, spastic colon and inflammatory bowel disease), inflammation and scarring.

Recent studies have shown that activation of platelets by collagen is mediated through the same pathway used by immune receptors, with an immunoreceptor tyronsine kinase motif on the FcRγ playing a pivotal role (Watson & Gibbons, 1998, Immunol. Today 19:260-264), and also that FcRγ plays a pivotal role in the generation of neointimal hyperplasia following balloon injury in mice, most likely through collagen-induced activation of platelets and leukocyte recruitment (Konishi et al., 2002, Circulation 105:912-916). Thus, the prodrugs described herein can also be used to inhibit collagen-induced platelet activation and to treat or prevent diseases associated with or caused by such platelet activation, such as, for example, intimal hyperplasia and restenosis following vascular injury.

In addition to the myriad diseases discussed above, cellular and animal empirical data confirm that the active 2,4-pyrimidinediamine compounds described in U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603),international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893) are also useful for the treatment or prevention of autoimmune diseases, as well as the various symptoms associated with such diseases. Thus, prodrugs of these active compounds are useful for treating or preventing such diseases and/or symptoms. The types of autoimmune diseases that may be treated or prevented with such prodrugs generally include those disorders involving tissue injury that occurs as a result of a humoral and/or cell-mediated response to immunogens or antigens of endogenous and/or exogenous origin. Such diseases are frequently referred to as diseases involving the nonanaphylactic (i.e., Type II, Type III and/or Type IV) hypersensitivity reactions.

As discussed previously, Type I hypersensitivity reactions generally result from the release of pharmacologically active substances, such as histamine, from mast and/or basophil cells following contact with a specific exogenous antigen. As mentioned above, such Type I reactions play a role in numerous diseases, including allergic asthma, allergic rhinitis, etc.

Type II hypersensitivity reactions (also referred to as cytotoxic, cytolytic complement-dependent or cell-stimulating hypersensitivity reactions) result when immunoglobulins react with antigenic components of cells or tissue, or with an antigen or hapten that has become intimately coupled to cells or tissue. Diseases that are commonly associated with Type II hypersensitivity reactions include, but are not limited, to autoimmune hemolytic anemia, erythroblastosis fetalis and Goodpasture's disease.

Type III hypersensitivity reactions, (also referred to as toxic complex, soluble complex, or immune complex hypersensitivity reactions) result from the deposition of soluble circulating antigen-immunoglobulin complexes in vessels or in tissues, with accompanying acute inflammatory reactions at the site of immune complex deposition. Non-limiting examples of prototypical Type III reaction diseases include the Arthus reaction, rheumatoid arthritis, serum sickness, systemic lupus erythematosis, certain types of glomerulonephritis, multiple sclerosis and bullous pemphingoid.

Type IV hypersensitivity reactions (frequently called cellular, cell-mediated, delayed, or tuberculin-type hypersensitivity reactions) are caused by sensitized T-lymphocytes which result from contact with a specific antigen. Non-limiting examples of diseases cited as involving Type IV reactions are contact dermatitis and allograft rejection.

Autoimmune diseases associated with any of the above nonanaphylactic hypersensitivity reactions may be treated or prevented with the prodrugs according to structural formulae (I) and (Ia). In particular, the methods may be used to treat or prevent those autoimmune diseases frequently characterized as single organ or single cell-type autoimmune disorders including, but not limited to: Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis,

autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, ulcerative colitis and membranous glomerulopathy, as well as those autoimmune diseases frequently characterized as involving systemic autoimmune disorder, which include but are not limited to: systemic lupus erythematosis (SLE), rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, multiple sclerosis and bullous pemphigoid.

It will be appreciated by skilled artisans that many of the above-listed autoimmune diseases are associated with severe symptoms, the amelioration of which provides significant therapeutic benefit even in instances where the underlying autoimmune disease may not be ameliorated. Many of these symptoms, as well as their underlying disease states, result as a consequence of activating the FcγR signaling cascade in monocyte cells. As the prodrugs of structural formulae (I) and (Ia) metabolize to 2,4-pyrimidinediamine compounds that are potent inhibitors of such FcγR signaling in monocytes and other cells, the methods find use in the treatment and/or prevention of myriad adverse symptoms associated with the above-listed autoimmune diseases.

As a specific example, rheumatoid arthritis (RA) typically results in swelling, pain, loss of motion and tenderness of target joints throughout the body. RA is characterized by chronically inflamed synovium that is densely crowded with lymphocytes. The synovial membrane, which is typically one cell layer thick, becomes intensely cellular and assumes a form similar to lymphoid tissue, including dendritic cells, T-, B- and NK cells, macrophages and clusters of plasma cells. This process, as well as a plethora of immunopathological mechanisms including the formation of antigen-immunoglobulin complexes, eventually result in destruction of the integrity of the joint, resulting in deformity, permanent loss of function and/or bone erosion at or near the joint. The methods may be used to treat or ameliorate any one, several or all of these symptoms of RA. Thus, in the context of RA, the methods are considered to provide therapeutic benefit (discussed more generally, infra) when a reduction or amelioration of any of the symptoms commonly associated with RA is achieved, regardless of whether the treatment results in a concomitant treatment of the underlying RA and/or a reduction in the amount of circulating rheumatoid factor ("RF").

The American College of Rheumatology (ACR) has developed criteria for defining improvement and clinical remission in RA. Once such parameter, the ACR20 (ACR criteria for 20% clinical improvement), requires a 20% improvement in the tender and swollen joint count, as well as a 20% improvement in 3 of the following 5 parameters: patient's global assessment, physician's global assessment, patient's assessment of pain, degree of disability, and level of acute phase reactant. These criteria have been expanded for 50% and 70% improvement in ACR50 and ACR70, respectively. Other criteria includes Paulu's criteria and radiographic progression (e.g. Sharp score).

In some embodiments, therapeutic benefit in patients suffering from RA is achieved when the patient exhibits an ARC20. In specific embodiments, ARCs of ARC50 or even ARC70 may be achieved.

Systemic lupus erythematosis ("SLE") is typically associated with symptoms such as fever, joint pain (arthralgias), arthritis, and serositis (pleurisy or pericarditis). In the context of SLE, the methods are considered to provide therapeutic benefit when a reduction or amelioration of any of the symptoms commonly associated with SLE are achieved, regardless of whether the treatment results in a concomitant treatment of the underlying SLE.

Multiple sclerosis ("MS") cripples the patient by disturbing visual acuity; stimulating double vision; disturbing motor functions affecting walking and use of the hands; producing bowel and bladder incontinence; spasticity; and sensory deficits (touch, pain and temperature sensitivity). In the context of MS, the methods are considered to provide therapeutic benefit when an improvement or a reduction in the progression of any one or more of the crippling effects commonly associated with MS is achieved, regardless of whether the treatment results in a concomitant treatment of the underlying MS.

When used to treat or prevent such diseases, the prodrugs described herein may be administered singly, as mixtures of one or more prodrugs or in mixture or combination with other agents useful for treating such diseases and/or the symptoms associated with such diseases. The prodrugs may also be administered in mixture or in combination with agents useful to treat other disorders or maladies, such as steroids, membrane stabilizers, 5LO inhibitors, leukotriene synthesis and receptor inhibitors, inhibitors of IgE isotype switching or IgE synthesis, IgG isotype switching or IgG synthesis, β-agonists, tryptase inhibitors, aspirin, COX inhibitors, methotrexate, anti-TNF drugs, retuxin, PD4 inhibitors, p38 inhibitors, PDE4 inhibitors, and antihistamines, to name a few. The prodrugs may be administered in the form of compounds per se, or as pharmaceutical compositions comprising a prodrug.

Pharmaceutical compositions comprising the prodrug(s) may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making levigating, emulsifying, encapsulating, entrapping or lyophilization processes. The compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the prodrugs into preparations which can be used pharmaceutically.

The prodrug may be formulated in the pharmaceutical composition per se, or in the form of a hydrate, solvate, N-oxide or pharmaceutically acceptable salt, as previously described. Typically, such salts are more soluble in aqueous solutions than the corresponding free acids and bases, but salts having lower solubility than the corresponding free acids and bases may also be formed.

Pharmaceutical compositions may take a form suitable for virtually any mode of administration, including, for example, topical, ocular, oral, buccal, systemic, nasal, injection, transdermal, rectal, vaginal, etc., or a form suitable for administration by inhalation or insufflation.

For topical administration, the prodrug(s) may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

Systemic formulations include those designed for administration by injection, e.g., subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal oral or pulmonary administration.

Useful injectable preparations include sterile suspensions, solutions or emulsions of the active compound(s) in aqueous or oily vehicles. The compositions may also contain formulating agents, such as suspending, stabilizing and/or dispersing agent. The formulations for injection may be presented in unit dosage form, e.g., in ampules or in multidose containers, and may contain added preservatives.

Alternatively, the injectable formulation may be provided in powder form for reconstitution with a suitable vehicle, including but not limited to sterile pyrogen free water, buffer,

dextrose solution, etc., before use. To this end, the active compound(s) may be dried by any art-known technique, such as lyophilization, and reconstituted prior to use.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art.

For oral administration, the pharmaceutical compositions may take the form of, for example, lozenges, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium tearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or etting agents (e.g., sodium lauryl sulfate). The tablets may be coated by methods well known in the art with, for example, sugars, films or enteric coatings. Phosphate prodrugs in which the progroup(s) is of the formula $—(CR^dR^d)_y—O—P(O)(OH)_2$, where each R^d is, independently of the others, selected from hydrogen and lower alkyl and y is 1 or 2 and that exhibit a water-solubility in the range of about 0.1 to 1000 mg/ml at physiological pH are especially suited for oral administration via tablets and capsules. When administered t Sprague-Dawley rats orally from capsules, prodrug Compound 4 exhibits a bioavailability of drug Compound 1 of about 30% (see FIG. **5**), with absorption being nearly identical to that of active drug Compound 1 (see FIG. **6**). Other phosphate prodrugs having water-solubility properties similar to those of prodrug Compound 4 are expected to exhibit similar pharmacokinetic properties.

A specific exemplary tablet formulation for prodrug Compound 4 (as well as other phosphate-containing prodrugs) contains about 50-400 mg prodrug compound (or a salt thereof), about 0.05 to 0.5 wt % colloidal silicon dioxide, about 0.5 to 5.0 wt % croscarmellose sodium, about 0.25 to 5.0 wt % magnesium stearate and about 20 to 80 wt % microcrystalline cellulose. If desired, the tablets can be coated with a film, such as a hypromellose film carboxymethyl cellulose or fructose, which can optionally contain coloring agents, such as for example FD&C blue #1, PD&C green #3, FD&C yellow #6 and titanium dioxide.

Liquid preparations for oral administration may take the form of, for example, elixirs, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol, cremophore™ or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, preservatives, flavoring, coloring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the prodrug, as is well known.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For rectal and vaginal routes of administration, the prodrug(s) may be formulated as solutions (for retention enemas) suppositories or ointments containing conventional suppository bases such as cocoa butter or other glycerides.

For nasal administration or administration by inhalation or insufflation, the prodrug(s) can be conveniently delivered in the form of an aerosol spray from pressurized packs or a nebulizer with the use of a suitable propellants e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, fluorocarbons, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges for use in an inhaler or insufflator (for example capsules and cartridges comprised of gelatin) may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

For ocular administration, the prodrug(s) may be formulated as a solution, emulsion, suspension, etc. suitable for administration to the eye. A variety of vehicles suitable for administering compounds to the eye are known in the art. Specific non-limiting examples are described in U.S. Pat. Nos. 6,261,547; 6,197,934; 6,056,950; 5,800,807; 5,776,445; 5,698,219; 5,521,222; 5,403,841; 5,077,033; and 4,738,851.

For prolonged delivery, the prodrug(s) can be formulated as a depot preparation for administration by implantation or intramuscular injection. The prodrug(s) may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, e.g., as a sparingly soluble salt. Alternatively, transdermal delivery systems manufactured as an adhesive disc or patch which slowly releases the prodrug(s) for percutaneous absorption may be used. To this end, permeation enhancers may be used to facilitate transdermal penetration of the prodrug(s). Suitable transdermal patches are described in for example, U.S. Pat. Nos. 5,407,713; 5,352,456; 5,332,213; 5,336,168; 5,290,561; 5,254,346; 5,164,189; 5,163,899; 5,088,977; 5,087,240; 5,008,110; and 4,921,475.

Alternatively, other pharmaceutical delivery systems may be employed. Liposomes and emulsions are well-known examples of delivery vehicles that may be used to deliver prodrug(s). Certain organic solvents such as dimethylsulfoxide (DMSO) may also be employed, although usually at the cost of greater toxicity.

The pharmaceutical compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the prodrug(s). The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

6.6 Effective Dosages

The prodrug(s) described herein, or compositions thereof, will generally be used in an amount effective to achieve the intended result, for example in an amount effective to treat or prevent the particular disease being treated. The prodrug(s) may be administered therapeutically to achieve therapeutic benefit or prophylactically to achieve prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated and/or eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient may still be afflicted with the underlying disorder. For example, administration of a compound to a patient suffering from an allergy provides therapeutic benefit not only when the underlying allergic response is eradicated or ameliorated, but also when the patient reports a decrease in the severity or duration of the symptoms associated with the allergy follow-

ing exposure to the allergen. As another example, therapeutic benefit in the context of asthma includes an improvement in respiration following the onset of an asthmatic attack, or a reduction in the frequency or severity of asthmatic episodes. Therapeutic benefit in the context of RA also includes the ACR20, or ACR50 or ACR70, as previously described. Therapeutic benefit also generally includes halting or slowing the progression of the disease, regardless of whether improvement is realized.

For prophylactic administration, the prodrug(s) may be administered to a patient at risk of developing one of the previously described diseases. For example, if it is unknown whether a patient is allergic to a particular drug, the prodrug(s) may be administered prior to administration of the drug to avoid or ameliorate an allergic response to the drug. Alternatively, prophylactic administration may be applied to avoid the onset of symptoms in a patient diagnosed with the underlying disorder. For example, the prodrug(s) may be administered to an allergy sufferer prior to expected exposure to the allergen. Prodrug(s) may also be administered prophylactically to healthy individuals who are repeatedly exposed to agents known to one of the above-described maladies to prevent the onset of the disorder. For example, prodrug(s) may be administered to a healthy individual who is repeatedly exposed to an allergen known to induce allergies, such as latex, in an effort to prevent the individual from developing an allergy. Alternatively, prodrug(s) may be administered to a patient suffering from asthma prior to partaking in activities which trigger asthma attacks to lessen the severity of, or avoid altogether, an asthmatic episode.

The amount of prodrug(s) administered will depend upon a variety of factors, including, for example, the particular indication being treated, the mode of administration, whether the desired benefit is prophylactic or therapeutic, the severity of the indication being treated and the age and weight of the patient, the bioavailability of the particular prodrug(s) the conversation rate and efficiency into active drug compound under the selected route of administration, etc. Determination of an effective dosage of prodrug(s) for a particular use and mode of administration is well within the capabilities of those skilled in the art.

Effective dosages may be estimated initially from in vitro activity and metabolism assays. For example, an initial dosage of prodrug for use in animals may be formulated to achieve a circulating blood or serum concentration of the metabolite active compound that is at or above an IC_{50} of the particular compound as measured in as in vitro assay, such as the in vitro CHMC or BMMC and other in vitro assays described in U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Ser. No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893). Calculating dosages to achieve such circulating blood or serum concentrations taking into account the bioavailability of the particular prodrug via the desired route of administration is well within the capabilities of skilled artisans. For guidance, the reader is referred to Fingl & Woodbury, "General Principles," In: Goodman and Gilman's The Pharmaceutical Basis of Therapeutics, Chapter 1, pp. 1-46, latest edition, Pagamonon Press, and the references cited therein.

Initial dosages of prodrug can also be estimated from in vivo data, such as animal models. Animal models useful for testing the efficacy of the active metabolites to treat or prevent the various diseases described above are well-known in the art. Suitable animal models of hypersensitivity or allergic reactions are described in Foster, 1995, Allergy 50(21Suppl): 6-9, discussion 34-38 and Tumas et al., 2001, J. Allergy Clin. Immunol. 107(6):1025-1033. Suitable animal models of allergic rhinitis are described in Szelenyi et al., 2000, Arzneimittelforschung 50(11):1037-42; Kawaguchi et al., 1994, Clin. Exp. Allergy 24(3):238-244 and Sugimoto et al., 2000, Immunopharmacology 48(l):1-7. Suitable animal models of allergic conjunctivitis are described in Carreras et al., 1993, Br. J. Ophthalmol. 77(8):509-514; Saiga et al., 1992, Ophthalmic Res. 24(1):45-50; and Kunert et al., 2001, Invest. Ophthalmol. Vis. Sci. 42(11):2483-2489. Suitable animal models of systemic mastocytosis are described in O'Keefe et al., 1987, J. Vet. Intern. Med. 1(2):75-80 and Bean-Knudsen et al., 1989, Vet. Pathol. 26(l):90-92. Suitable animal models of hyper IgE syndrome are described in Claman et al., 1990, Clin. Immunol. Immunopathol. 56(1):46-53. Suitable animal models of B-cell lymphoma are described in Hough et al., 1998, Proc. Natl. Acad. Sci. USA 95:13853-13858 and Hakim et al., 1996, J. Immunol. 157(12):5503-551 1. Suitable animal models of atopic disorders such as atopic dermatitis, atopic eczema and atopic asthma are described in Chan et al., 2001, J. Invest. Dermatol. 1 17(4):977-983 and Suto et al., 1999, Int. Arch. Allergy Immunol. 120(Suppl 1):70-75. Animal models suitable for testing the bioavailability and/or metabolism of prodrugs into active metabolites are also well-known. Ordinarily skilled artisans can routinely adapt such information to determine dosages of particular prodrugs suitable for human administration. Additional suitable animal models are described in the Examples section.

Dosage amounts will typically be in the range of from about 0.0001 mg/kg/day, 0.001 mg/kg/day or 0.01 mg/kg/day to about 100 mg/kg/day, but may be higher or lower, depending upon, among other factors, the activity of the active metabolite compound, the bioavailability of the prodrug, its metabolism kinetics and other pharmacokinetic properties, the mode of administration and various other factors, discussed above. Dosage amount and interval may be adjusted individually to provide plasma levels of the prodrug(s) and/or active metabolite compound(s) which are sufficient to maintain therapeutic or prophylactic effect. For example, the prodrugs may be administered once per week, several times per week (e.g., every other day), once per day or multiple times per day, depending upon, among other things, the mode of administration, the specific indication being treated and the judgment of the prescribing physician. In cases of local administration or selective uptake, such as local topical administration, the effective local concentration of prodrug(s) and/or active metabolite compound(s) may not be related to plasma concentration. Skilled artisans will be able to optimize effective local dosages without undue experimentation.

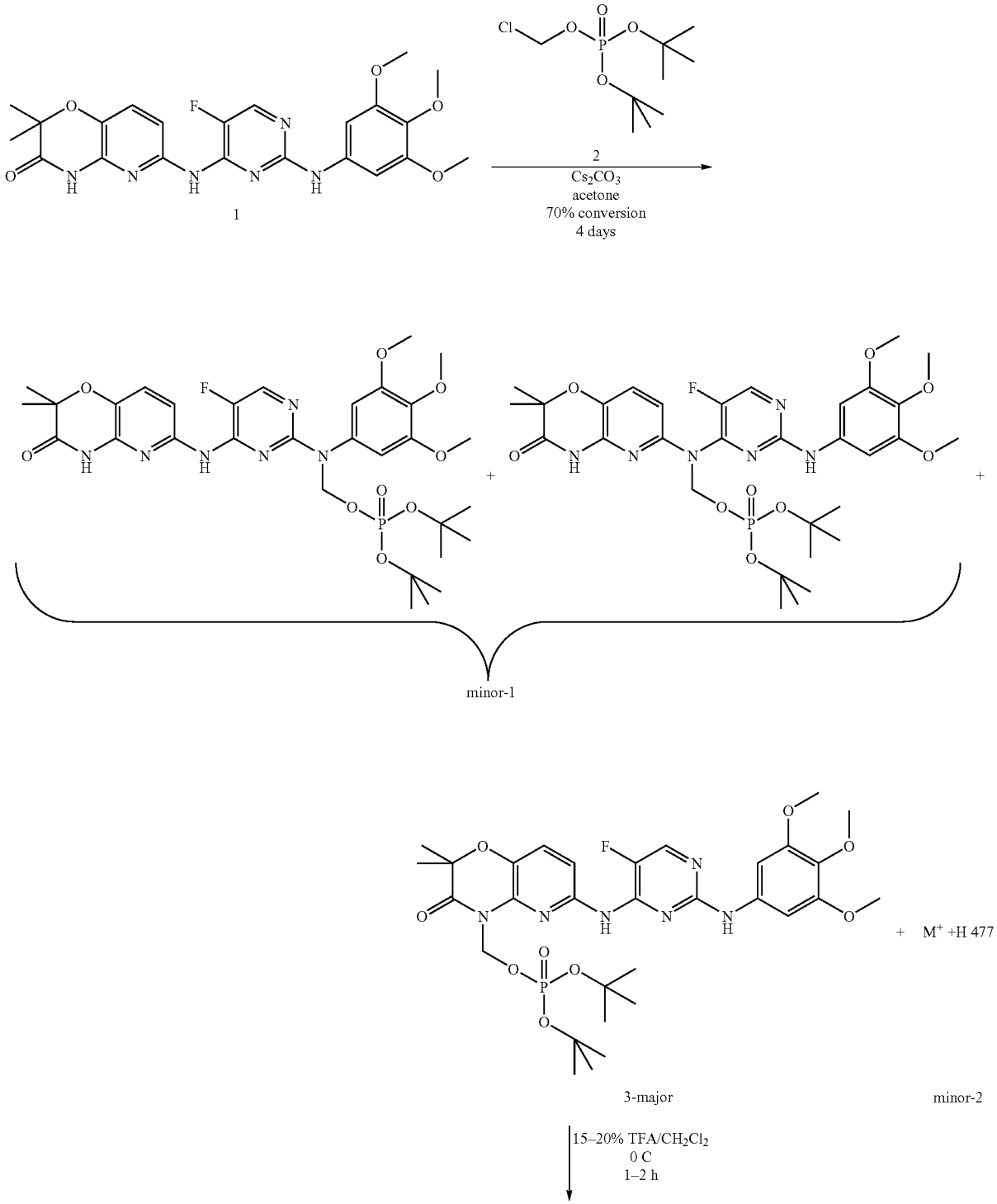
Preferably, the prodrugs will metabolize into active compound(s) that will provide therapeutic or prophylactic benefit without causing substantial toxicity. Toxicity of the active and other metabolites, as well as the unmetabolized prodrug may be determined using standard pharmaceutical procedures. The dose ratio between toxic and therapeutic (or prophylactic) effect is the therapeutic index. Prodrug(s) that exhibit high therapeutic indices are preferred.

The inventions having been described, the following examples are offered by way of illustration and not limitation.

7. EXAMPLES

7.1 Synthesis of Prodrug Compound 4

7.1.1 N4-(2,2-dimethyl-4-[(di-tert-butyl phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 3)



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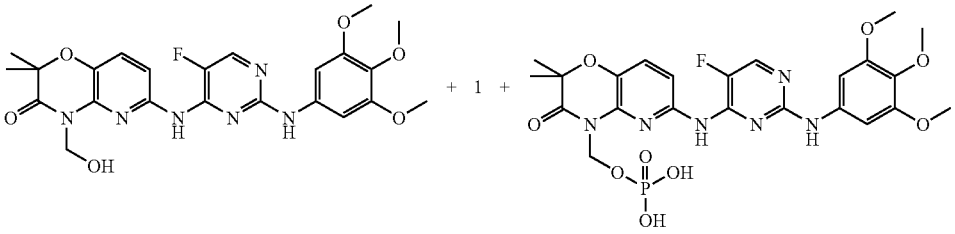

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N4-(2,2-dimethyl-3-oxo-4H-5-pyrido [1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (1, 1.0 g, 2.12 mmol), Cs_2CO_3 (1.0 g, 3.07 mmol) and di-tert-butyl chioromethyl phosphate (2, 0.67 g, 2.59 mmol) in acetone (20 mL) was stirred at room temperature under nitrogen atmosphere. Progress of the reaction was monitored by LC/MS. Crude reaction mixture displayed three product peaks with close retention times with M^++H 693 (minor-1), 693 (major; 3) and 477 (minor-2) besides starting material (Compound 1). Upon stirring the contents for 4 days (70% consumption), the reaction mixture was concentrated and diluted with water. The resultant pale yellow precipitate formed was collected by filtration and dried. The crude solid was purified by silica gel (p)retreated with 10% NEt_3/CH_2Cl_2 followed by eluting with hexanes) column chromatography by gradient elution with 70% EtOAc/hexanes-100% BtOAc). The fractions containing Compound 1 and M^++H 693 were collected and concentrated. The resulting crude white solid was subjected to repurification in the similar manner as described previously but by eluting with 30%-50%-75%-100% EtOAc/hexanes. The major product eak with M^++H 693 was collected as a white solid (270 mg, 18%) and was characterized as 4-(2,2-dimethyl-4-[(di-tert-butyl phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 3). ^{1}H NMR (DMSO-d6): δ 9.21 (s, 1H), 9.17 (s, 1H), 8.16 (d, 1H, J=2.6 Hz), 7.76 (d, 1H, J=8.5 Hz), 7.44 (d, 1H, J=8.5 Hz), 7.02 (s, 2H), 5.78 (d, 1H, J^3PH=6.1 Hz), 3.64 (s, 6H), 3.58 (s, 3H), 1.45 (s, 6H), 1.33 (s, 9H). LCMS: ret. time: 14.70 min.; purity: 95%; MS (m/e): 693 (MH^+). ^{31}P NMR (DMSO-d6): −11.36.

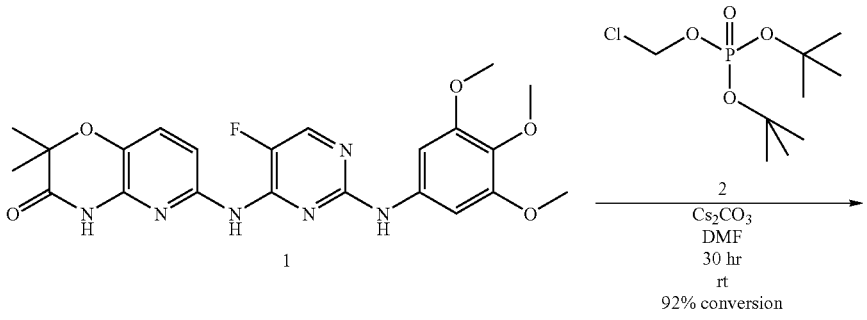
7.1.2 N4-(2,2-dimethyl-4-1(dihydrogen phosphonoxy)methyll-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 4)

Trifluoroacetic acid (1.5 mL) was added dropwise as a neat for 5 min to N4-(2,2-dimethyl-4-[(di-tert-butyl phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 3, 120 mg, 0.173 mmol) dissolved in CH_2Cl_2 (10 mL) at 0° C. under nitrogen atmosphere. The contents were allowed to stir for 1.5 h. Progress of the reaction mixture was monitored by LC/MS. After complete consumption of the starting material, reaction mixture was concentrated, dried and triturated with ether. The ethereal layer was decanted and dried to provide the crude solid. LC/MS analysis of the crude displayed three peaks with M^++H 581, 471 and 501. The peak corresponding to M^++H 581 was collected by preparative HPLC chromatographic purification. The fractions were lyophilised and dried to provide 53 mg (52%) of off white fluffy solid and characterized as N4-(2,2-dimethyl-4-[(dihydrogen phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 4). ^{1}H NMR (DMSO-d6): δ 9.21 (br s, 2H), 8.16 (d, 1H, J 2.6 Hz), 7.93 (d, 1H, J=8.5 Hz), 7.39 (d, 1H, J=8.5 Hz), 7.05 (s, 2H), 5.79 (d, 1H, J^3_{PH}=6.6 Hz), 3.67 (s, 6H), 3.59 (s, 3H), 1.44 (s, 6H). LCMS: ret. time: 8.52 min.; purity: 95%; MS (m/e): 581 (MH^+). ^{31}P NMR (DMSO-d6): −2.17.

7.2 Alternative Synthesis of Prodrug Compound 4

An alternative method of synthesizing prodrug Compound 4 which alleviates the need for column chromatography and HPLC purification is provided below.

7.2.1 Synthesis of N4-(2,2-dimethyl-4-[(di-tert-butyl phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 3)



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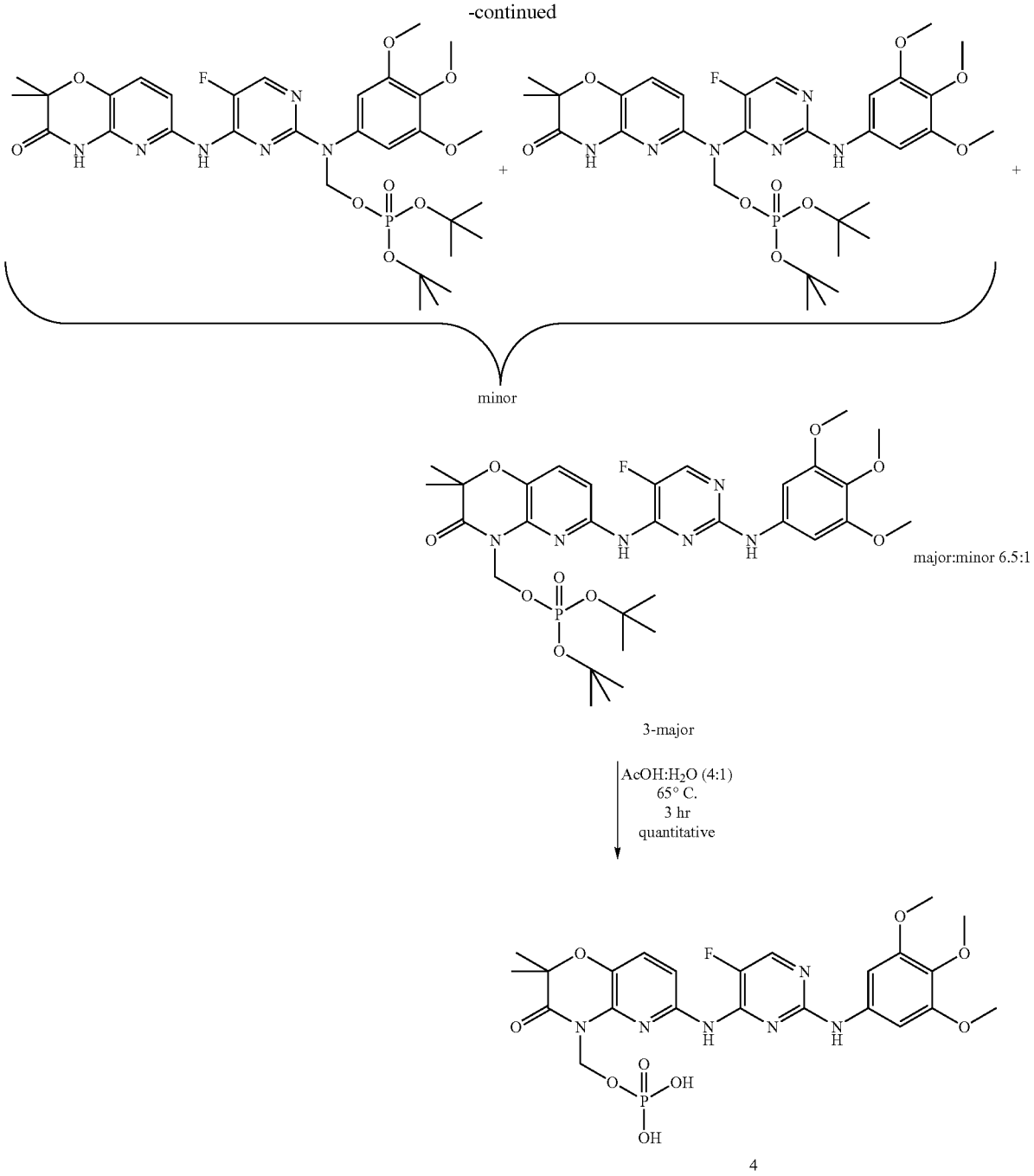


N4-(2,2-dimethyl-3-oxo-4H-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 1, 19.73 g, 41.97 mmol), Cs_2CO_3 (15.04 g, 46.16 mmol) and di-tert-butyl chloromethyl phosphate (13.0 g, 50.38 mmol) in DMF (100 mL) was stirred at room temperature under nitrogen atmosphere. Progress of the reaction was monitored by in process LC/MS. Crude reaction mixture displayed two product peaks (ratio 1:6.5) with close retention times displaying M^++H 693 (minor) and 693 (major) besides starting material (Compound 1). Initial yellow reaction mixture turned to olive green as the reaction progressed. Workup is carried out as follows

1). Upon stirring the contents for 30 h (92% consumption), reaction mixture was poured onto ice-water (400 mL) and stirred the contents by adding brine solution (200 mL). Fine yellow tan solid formed was filtered, washed with water and dried overnight.

2). The solid (35 g) was dissolved in MTBE (500 mL) and washed with water (400 mL). Aqueous layer was extracted with MTBE (2×350 mL) till the absence of UV on TLC. Combined organic layers were dried over anhydrous Na_2SO_4 and decanted. Note: step 2 can be done directly, however, DMF extraction back into solution leads to difficulty in the crystallization step.

3). The dark red clear solution was subjected to 10 g of activated charcoal treatment, heated to boil and filtered.

4). The dark red clear solution was concentrated by normal heating to 400 mL of its volume and left for crystallization. The solid crystallized as granules was filtered, crushed the granules to powder, washed with MTBE (400 mL) and dried under high vacuum. See step 7 for the workup of mother liquor. Weight of the solid: 17 g; purity: 90% (Compound 3), 6.26% (Compound 1), 1.8% (minor M+693).

5). At this stage solid was taken in 500 ml of ethylether and heated to boil. Cooled and filtered to remove undissolved material. Filtrate was concentrated.

6). Above concentrate was subjected to crystallization in MTBE (300 mL). The white solid formed was filtered, washed with MTBE (100 mL) and dried under high vacuum to provide the desired N4-(2,2-dimethyl-4-[(di-tert-butyl phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 3) in 97% purity. ^{1}H NMR (DMSO-d6): 6 9.21 (s, 1H), 9.17 (s, 1H), 8.16 (d, 1H, J=2.6 Hz), 7.76 (d, 1H, J=8.5 Hz), 7.44 (d, 1H, J=8.5 Hz), 7.02 (s, 2H), 5.78 (d, 1H, J^3_{PH}=6.1 Hz), 3.64 (s, 6H), 3.58 (s, 3H), 1.45 (s, 6H), 1.33 (s, 9H). LCMS: ret. time. 14.70 min.; purity: 95%; MS (m/e): 693 (MH^+). ^{31}P NMR (DMSO-d6): −11.36. Weight of the solid: 15.64 g (yield: 55%); purity: 97% (R935787), 3% (Compound 1).

7). Mother liquor was concentrated and steps 5 and 6 were repeated to provide Compound 3.

7.2.2 Synthesis of N4-(2,2-dimethyl-4-[(dihydrogen phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 4)

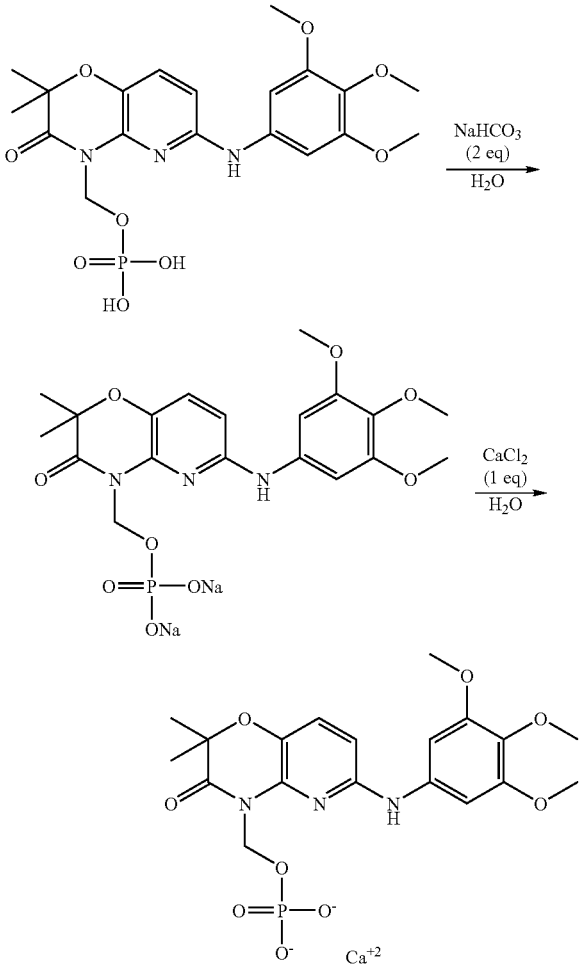
N4-(2,2-dimethyl-4-[(di-tert-butyl phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 3); (15.0 g, 21.67 mmol) dissolved in AcOH:H_20 (225 mL, 4:1) was heated at 65 ° C. (oil bath temp). The progress of the reaction was monitored by in process LC/MS. The reaction mixture transformed to faint tan white solid after 1 h of heating. At this point most of Compound 3 converted to mono des t-butyl product. After 3 h of heating, consumption of SM and complete conversion of intermediate (mono des t-butylated) to product was observed.

Reaction mixture was cooled, poured onto ice-water (200 mL), stirred for 20 min and filtered. The clear white filter cake was washed with water (600 ml) and acetone (200 mL) successively, dried for 2h followed by drying under high vacuum over P_2O_5 in a desiccator. Weight of the solid: 12.70 g; purity: 97% (Compound 3) and 3% (Compound 1) ^{1}H NMR indicated acetic acid presence (1:1)

To remove acetic acid, the solid was taken in acetonitrile (300 mL) and concentrated by rotovap vacuum. This process was repeated 2 times with acetonitrile and toluene (3×300 mL). The solid obtained was dried under high vacuum at 50° C.

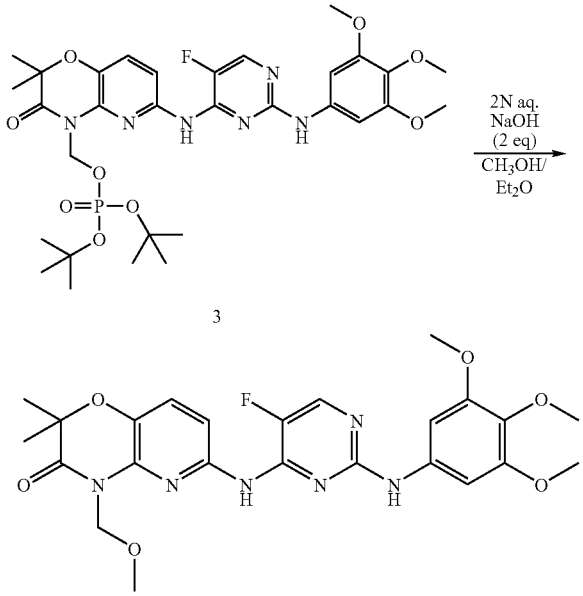
Finally, the solid was taken in acetone (400 mL), filtered and dried to provide N4-(2,2-dimethyl-4-[(dihydrogen phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 4). ^{1}H NMR (DMSO-d6): δ 9.21 (br s, 2H), 8.16 (d, 1H, J=2.6 Hz), 7.93 (d, 1H, J=8.5 Hz), 7.39 (d, 1H, J=8.5 Hz), 7.05 (s, 2H), 5.79 (d, 1H, J^3_{PH}=6.6 Hz), 3.67 (s, 6H), 3.59 (s, 3H), 1.44 (s, 6H), LCMS: ret. time: 8.52 min.; purity: 95%; MS (m/e): 581 (MH^+). ^{31}P NMR (DMSO-d6): −2.17.

7.3 Synthesis of N4-(2,2-dimethyl-4-[(dihydrogen phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine mono calcium salt (Compound 6)



Aqueous (10 mL) $NaHCO_3$ (0.17 g, 2.02 mmol) solution was added dropwise to a suspension of N4-(2,2-dimethyl-4-[(dihydrogen phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3 ,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (0.5 g, 0.86 mmol) in water (5 mL) at room temperature while stirring the contents. The clear solution formed was treated with aqueous (10 mL) $CaCl_2$ (0.11 g in 10 mL water, 0.99 mmol) in a dropwise manner at room temperature. The addition resulted in the precipitation of a white solid from reaction mixture. Upon completion of addition, the contents were stirred for a period of 30 min, filtered, washed with water (40 mL) and dried. The clear white solid was taken in water (30 mL) and heated on a stir plate to boil. The solution was cooled, filtered and dried. The white solid collected and further dried under high vacuo at 80° C. for 32 h to provide 0.41 g (83%) of N4-(2,2-dimethyl-4-[(dihydrogen phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine mono calcium salt (Compound 6).

7.4 Synthesis of Prodrug Compound 8



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N4-(2,2-dimethyl-4-[(di-tert-butyl phosphonoxy)methyl]-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (prepared as described above) (0.2 g, 0.29 mmol) was added to a mixture of MeOH(5 mL) and Et_2O (5 mL). 2N aq. NaOH (0.023 g, 0.58 mmol) was added at once while stirring the contents at room temperature. Progress of the reaction was monitored by LC/MS. After 8h of stirring, the solid precipitated was filtered and dried to provide N4-(2,2-dimethyl-4-methoxymethyl-3-oxo-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (Compound 8) as a white solid (0.11 g, 74%). ^{1}H NMR (DMSO-d6): 6 9.47 (s, 1H), 9.15 (s, 1H), 8.16 (d, 1H, J=3.8 Hz), 7.87 (d, 1H, J=8.5 Hz), 7.37 (d, 1H, J=8.5 Hz), 7.03 (s, 2H), 5.40 (s, 2H), 3.66 (s, 6H), 3.59 (s, 3H), 3.27 (s, 3H), 1.44 (s, 6H). LCMS: ret. time: 12.88 min.; purity: 92%; MS (m/e): 515 (MH^+).

7.5 The Active 2,4-Pyrimidinediamine Compounds are Tolerated in Animals

The ability of numerous biologically active 2,4-pyrimidinediamine compounds to exert their activity at doses below those exhibiting toxicity in animals has been demonstrated previously (see, e.g., U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Ser. No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003 (U.S.2007/0060603), international application Ser. No. PCT/US03/24087 (WO2004/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004 (US2005/0234049), and international application Ser. No. PCT/US2004/24716 (WO/2005/016893).

The safety pharmacology of active Compound 1 has been studied in a core battery of studies (respiratory, CNS, cardiovascular, and HERG). A slight reduction in heart rate and increase in RR interval was noted at 50 mg/kg in the cardiovascular study and a slight effect on a few behavioral parameters at 50 mg/kg was also noted in the CNS (Irwin) study. Otherwise the safety pharmacology studies determined that Compound 1 was well tolerated. GLP toxicology studies included negative mutagenicity and clastogenicity studies (Ames, chromosomal aberration, and mouse micronucleus). In 28-day toxicity studies in rats and monkeys, higher doses had evidence of a reversible effect on hematology, liver transaminase (mild effect in the rat only), spleen and thymus size (rat only) and bone marrow cellularity (rat and monkey). Immunophenotyping in the rat study revealed a significant decrease in the percentage of CD3+ cells in high dose rats while a significant increase in CD45RA+ cells was noted following recovery. Histopathology was noteworthy only for mild reductions in marrow cellularity at high doses. There was no evidence for untoward effects on humoral immunity in the anti-KLH antibody assessment. The No Observed Adverse Effect Level (NOAEL) is 10-30 mg/kg/day for rats and 100 mg/kg/day for monkeys.

7.6 Drug Compound 1 is Biologically Active in In Vitro Assays

Compound 1 blocks FcεRI-dependent activation of Cord-Blood Derived Primary Human Mast Cells (CHMC) in a dose-dependent manner with an EC_{50} of approximately 43 nM as assessed by measuring the activity of tryptase released upon degranulation. Compound 1 does not inhibit ionomycin-induced degranulation of CHMCs. Ionomycin is a calcium ionophore that induces CHMC degranulation bypassing early FcR signaling, thus indicating that Compound 1 is specific to FcR signaling, and not degranulation per se. Compound 1 also inhibits the FcεRI-dependent production and release of LTC4 (EC_{50}=39 nM) and all cytokines tested (EC_{50} ranging from 158 nM-462 nM).

7.7 Drug Compound 1 is Effective in Animal Models of Rheumatoid Arthritis

The biologic activity of Compound 1 in IC-mediated vascular edema (Arthus reaction in the rat), in collagen antibody-induced arthritis in the mouse, and in a rat model of collagen-induced arthritis.

7.7.1 Arthus Reaction

IC-mediated acute inflammatory tissue injury is implicated in a variety of human autoimmune diseases, including vasculitis, serum sickness, systemic lupus erythematosus, RA, and glomerulonephritis. The classical experimental model for IC-mediated tissue injury is the Reverse Passive Arthus (RPA) reaction. Intravenous injection of antigen (ovalbumin, OVA) following intradermal injection of antibodies specific to OVA (rabbit anti-OVA IgG) results in perivascular deposition of IC and a rapid inflammatory response characterized by edema, neutrophil infiltration, and hemorrhage at the injection sites (Szalai, et al., 2000, J. Immunol. 164(1):463-468).

A single oral treatment of rats with Compound I one hour prior to antigen/antibody administration reduced the cutaneous RPA reaction and inflammatory edema in a dose-dependent manner. Administration of 10 mg/kg oral Compound 1 inhibited extravascular leakage of Evans blue dye (OD_{610}) from tissue biopsies by 80% compared with vehicle control.

7.7.2 Collagen Antibody-Induced Arthritis

The anti-inflammatory activity of Compound 1 was evaluated in the mouse collagen-antibody-induced arthritis (CAIA) model in which an anti-type II collagen antibody cocktail is applied to induce arthritis (Teroto et al., 1992, J.

Immunol. 148(7):2103-2108; McCoy et al., 2002, J. Clin. Invest. 110(5):651-658; Kagari et al., 2002, J. Immunol. 169 (3):1459-1466). This passive model differs from the traditional rodent collagen-induced arthritis (CIA) in that disease symptoms appear quickly (developing within 24-48 hrs after an IV-injection of antibodies), arthritis is inducible in both CIA-susceptible and CIA-resistant mouse strains, and it allows evaluation of inflammation that is independent of antibody production.

CAIA was induced in Balb/c mice by intravenous injection of Arthrogen-CIA® Monoclonal Antibody Blend (Chemicon International, Inc., Temecula, Calif.) via the tail vein, followed 2 days later by an intraperitoneal injection of LPS. Oral Compound 1 treatment was started within 4 hours of antibody administration (Day 0). The severity of the arthritis in hindpaws was scored daily (scale of 0-4 per paw, sum of scores for both hind paws). By Day 5, both control groups, saline and vehicle, reached their peak clinical score with a disease incidence of 100%. 1

Reduced inflammation and swelling was evident in animals treated with Compound 1, and the arthritis progressed more slowly. Treatment with Compound 1 (b.i.d.) significantly reduced clinical arthritis ($p<0.05$) compared with animals treated with vehicle only, while lower dose levels of Compound 1 showed a trend toward reduced arthritis severity, disease incidence, and time of onset; however, the differences were not significant ($p>0.05$).

7.7.3 Collagen-Induced Arthritis

One of the experimental models for IC-mediated tissue injury is the CIA in rodents (Kleinau et al., 2000, J. Exp. Med. 191:1611-1616). Injection of type II collagen (CII) into rodents produces an immune reaction that characteristically involves inflammatory destruction of cartilage and bone of the distal joints with concomitant swelling of surrounding tissues. CIA in rats is commonly used to evaluate compounds that might be of potential use as drugs for treatment of rheumatoid arthritis and other chronic inflammatory conditions and is induced in susceptible strains of either mice or rats by injection of CII in incomplete Freund's adjuvant (IFA). Administration of this emulsion gives rise to polyarthritis, characterized by synovial hyperplasia, infiltration of mononuclear cells, pannus formation, and destruction of cartilage and bone. It has been previously well documented that antibodies to CII are a prerequisite for CIA in mice, as B-cell deficient mice do not develop arthritis (Svensson et al., 1998, Clin. Exp. Immunol. 111:521-526).

Syngeneic LOU rats were immunized on Day 0 with native chicken CII/IFA. Oral treatment began at the onset of arthritis symptoms (Day 10). A total of 59 rats were treated with either a vehicle control or Compound 1 at one of four dose levels (1, 3, 10, and 30 mg/kg, q.d. by p.o. gavage). Hind limbs were scored daily for clinical arthritis severity using a standardized method based on the degree of joint inflammation. High resolution digital radiographs of hind limbs were obtained at the conclusion of the study (Day 28). These limbs were also analyzed for histopathologic changes. IgG antibodies to native CII were measured in quadruplicate by ELISA. There was a significant reduction ($p<0.05$) in arthritis severity that was evident within 7 days after initiation of therapy in the high-dose (30 mg/kg) group that continued to improve throughout the study. By Day 28, the clinical score in the animals treated with vehicle alone was 6.08±0.67 compared to 2.54±0.98 in the Compound 1 30 mg/kg group ($p<0.001$). Blinded radiographs at study termination (Day 28), demonstrated a significant reduction in joint damage: 3.66±0.71 (vehicle) vs. 1.63±0.67 (Compound 1) ($p<0.02$) (E. Brahn. 2004). Blinded composite histopathologic studies confirmed the regression of pannus and erosions: Mean modified Mankin scores were 11.8±0.9 (vehicle) vs. 3.7±0.9 (30 mg/kg Compound 1) ($p<0. 001$). Antibodies to native CII were not decreased in Compound 1-treated rats.

7.8 The Prodrug Compounds Are Orally Bioavailable

Prodrug Compound 4 was tested for oral bioavailability. For the study, the prodrug was dissolved in various vehicles (e.g. PEG 400 solution and CMC suspension) for intravenous and oral dosing in the rats. Where indicated, the active metabolite Compound 1 compound (drug) was formulated and administered in the same vehicles. Following administration of the prodrug and/or drug, plasma samples were obtained and extracted. The plasma concentrations of the prodrug and/or drug were determined by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) methods. Pharmacokinetic analyses were performed based on the plasma concentration data. The pharmacokinetic parameters of interest include Clearance (CL), Volume of distribution at steady-state (Vss), terminal half-life ($t_{1/2}$), and oral bioavailability (% F).

The results of these various pharmacokinetic experiments are illustrated in FIGS. **4-12**.

Referring to FIG. **4**, PK profiles are shown for IV and PO administration in Spraque-Dawley rats. For IV administration, Compound 4 was dissolved in PEG-400 and administered at a dose of 1 mg/kg. Rapid disappearance of prodrug Compound 4 was observed and drug Compound 1 was found in plasma samples obtained from the jugular vein. Given orally in the same vehicle, no prodrug Compound 4 was present systemically, but high levels of drug metabolite Compound 1 were observed.

FIG. **5** summarizes the PK parameters for the study described in FIG. **4**. Prodrug Compound 4 is rapidly cleared and, in part, converted to drug Compound 1. Given orally at a dose of 4 mg/kg, bioavailability was determined to be 29.9%. This bioavailability number is based on data obtained from a previous study (data not shown) in which drug Compound 1 was administered as an IV bolus dose at 1 mg/kg.

FIG. **6** compares drug Compound 1 exposure in Sprague-Dawley rats following oral administration of either drug Compound 1 (2.5 mg/kg in PEG-400) or prodrug Compound 4 (4 mg/kg in PEG-400). The values for AUC/dose are nearly identical indicating that the prodrug Compound 4 is absorbed equally as well as drug Compound 1.

FIG. **7** shows a plot of cLogD vs pH calculated using in-situ predictions for both Compound 1 and Compound 4. Compound 1 is highly liphophyllic and only weakly ionizable (measured solubility is less than 1 mcg/ml in phosphate buffer at pH=7.5, data not shown). In contrast, Compound 4 is highly polar at neutral pH. Measured solubility values are consistent with the predicted cLogD values at pH=7.5.

FIG. **8** demonstrates that prodrug Compound 4 is stable under acidic and neutral conditions at 37° C.

FIG. **9** illustrates the conversion of prodrug Compound 4 to drug Compound 1 in microsome preparations. Prodrug Compound 4 failed to convert to drug Compound 1 in microsomal preparations obtained from Xenotech. In follow-up studies using intestinal and hepatic microsomes obtained from a different source, conversion of Compound 4 to Compound 1 was observed (data not shown).

FIG. **10** illustrates that prodrug Compound 4 is unstable in rat plasma—hydrolysis to drug Compound 1 is observed and the conversion to Compound 1 is thought to be catalyzed by

phosphatase enzymes. The presence of Phosphatase activity in rat plasma was confirmed using p-nitrophenyl phosphate—a known substrate for phosphatase.

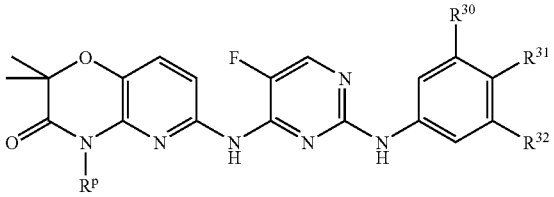
FIG. **11** illustrates the absorption of prodrug Compound 4 from different vehicles. Unlike drug Compound 1, absorption of prodrug Compound 4 is not dependent on formulation. Prodrug Compound 4 is absorbed equally well in solution formulations (PEG-400 and carboxymethylcellulose (CMC)) and as a powder in hard gelatin capsules.

Based on the pharmacokinetic data, the oral bioavailability (% F) of prodrug Compound 4 from all three vehicles tested (PEG-400 solution; CMC Solution; and powder in capsules) was determined to be approx. 30%.

What is claimed is:

1. A compound according to structural formula (IIIa):

(III)



or a pharmaceutically acceptable salt wherein R^p is $—CH_2—O—P(O)(OH)_2$.

2. The compound of claim **1** which is a pharmaceutically acceptable salt.

3. The compound of claim **2** which is an alkali metal salt.

4. The compound of claim **3** which is a sodium salt.

5. The compound of claim **4** which is a disodium salt.

6. The compound of claim **3** which is a potassium salt.

7. The compound of claim **6** which is a dipotassium salt.

8. The compound of claim **2** which is an alkaline earth metal salt.

9. The compound of claim **8** which is a calcium salt.

10. The compound of claim **8** which is a magnesium salt.

11. The compound of claim **2** which is an alkylamino salt.

12. The compound of claim **2** which is an ammonium salt.

13. N4-(2,2-dimethyl-4-[(dihydrogen phosphonoxy)methyl]-3-oxo-5-pyrido [1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine disodium salt hexahydrate.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

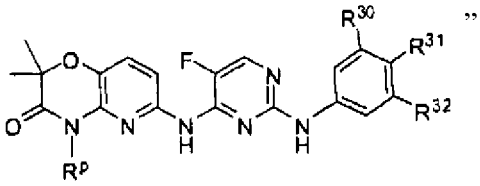
CERTIFICATE OF CORRECTION

PATENT NO. : 7,449,458 B2
APPLICATION NO. : 11/337049
DATED : November 11, 2008
INVENTOR(S) : Somasekhar Bhamidipati et al.

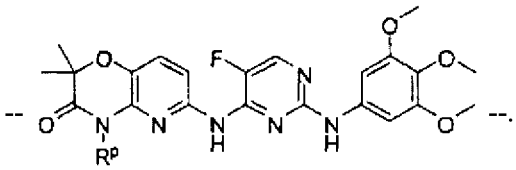
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1, at Column 75, Lines 16-25, please replace the formula:

(III)

“  ”

with the formula:

--  --.

IIIa

Claim 13, at Column 76, Line 22, please replace “5-pyrido [1,4]” with -- 5-pyrido[l,4] --.

Signed and Sealed this

Thirty-first Day of March, 2009

John Doll

JOHN DOLL
Acting Director of the United States Patent and Trademark Office

EXHIBIT B

US008263122B2

(12) **United States Patent**
Sun et al.

(10) **Patent No.: US 8,263,122 B2**
(45) **Date of Patent: Sep. 11, 2012**

(54) **WET GRANULATION USING A WATER SEQUESTERING AGENT**

(75) Inventors: **Thomas Sun**, Fremont, CA (US); **Ray Lo**, San Leandro, CA (US)

(73) Assignee: **Rigel Pharmaceuticals, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 748 days.

(21) Appl. No.: **12/266,337**

(22) Filed: **Nov. 6, 2008**

(65) **Prior Publication Data**

US 2009/0123539 A1 May 14, 2009

Related U.S. Application Data

(60) Provisional application No. 60/986,237, filed on Nov. 7, 2007.

(51) **Int. Cl.**
A61K 9/20 (2006.01)

(52) **U.S. Cl.** **424/464**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner — Robert A Wax
Assistant Examiner — Olga V Tcherkasskaya
(74) *Attorney, Agent, or Firm* — Travis Young; McDonnell Boehnen Hulbert & Berghoff LLP

(57) **ABSTRACT**

Disclosed are tablets comprising hydrolytically stable formulations of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt (Compound 1) prepared by a wet granulation process.

16 Claims, No Drawings

WET GRANULATION USING A WATER SEQUESTERING AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit under 35 U.S.C. §119(e) to application Ser. No. 60/986,237, filed Nov. 7, 2007, the content of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to pharmaceutical/formulation chemistry. The invention is understood to apply generally to formulations of hydrolytically unstable compounds. As a preferred embodiment, provided herein are higher density, hydrolytically stable formulations of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino) pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt (Compound 1) prepared by a wet granulation process. Such formulations inhibit degradation of Compound 1 during prolonged storage under ambient conditions. The formulations are useful for treating a variety of diseases including, but not limited to, lymphoma, immune (idiopathic) thrombocytopenia purpura (ITP), and rheumatoid arthritis (RA).

STATE OF THE ART

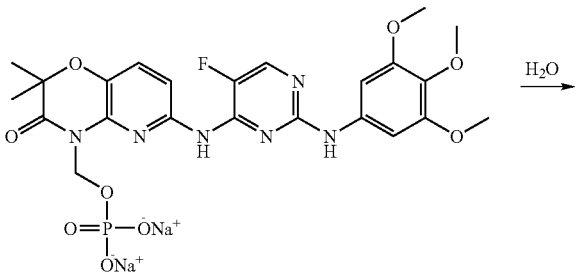
Compound 1 is currently in clinical studies for the treatment of a variety of diseases such as lymphoma, ITP and RA. Dosing is currently done with orally delivered tablets. Two sets of tablets used contain relatively high concentrations of Compound 1, i.e., 50 mg and 100 mg of active.

Compound 1, as synthesized, forms cotton like fluffy agglomerates with a very low bulk density (~0.15-0.30 g/mL). This characteristic confers poor powder flow and makes direct compression to tablets of the active impractical. Poor powder flow also results in a wide weight variation within the final product owing to variable fill of tablet dies, etc. Accordingly, it is desirable to formulate Compound 1 with higher density excipients such as fillers, binders, disintegrants, etc. which increase the bulk density and render the flow property adequate for compression into tablets.

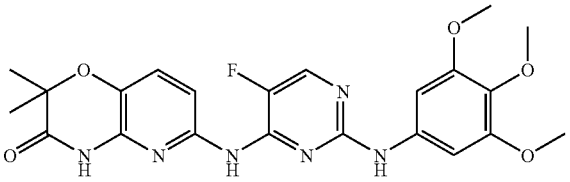
Granulation is a process well known in the pharmaceutical industry, involving the preparation of aggregates ("granules") of fine particles of materials. Such granules are often compacted to form tablets. Formulations of pharmaceutical powders are granulated for a variety of reasons falling into two main classes: processing and formulation. Processing reasons are exemplified by the need for densification and aggregation. A dense, granular material will flow more evenly and fill dies on high speed tablet machines better and with greater consistency than a simple mixture.

One method of making granules is so called "wet granulation." In its simplest form, wet granulation involves the addition of a granulating fluid, commonly water, functioning as a granulating liquid, to a stirred powder comprising the materials to be granulated. The granulating liquid can be used alone or as a solvent containing a binder (also referred to as a "dissolved adhesive") which is used to ensure particle adhesion once the granule is dry. If the drying and subsequent handling is done with care, the aggregates will retain their integrity, giving a material which is both denser and more free flowing than the original material. Wet granulation has also been carried out with organic solvents or water-organic solvent mixtures, but organic solvents can present fire or toxicity hazards.

Wet granulation adds a significant degree of difficulty especially where the active agent is sensitive to water or heat. This invention is contemplated for hydrolytically unstable compounds generally. Compound 1, including its hexahydrate, is water sensitive and undergoes decomposition according to the following reaction scheme:



Compound 1



Compound 2

Compound 1 is a prodrug of Compound 2. It is preferable, then, that any wet granulation process employing water be done in a manner where little or no degradation of Compound 1 occurs either during the granulation, tablet formation, or storage so as to ensure that the proper systemic levels of Compound 2 are achieved.

In addition, it is preferable that the tablets formed be of sufficient hardness that they can be hand manipulated without breakage but disintegrate rapidly upon administration.

SUMMARY OF THE INVENTION

This invention is generally directed to hydrolytically stable formulations of hydrolytically unstable compounds, in particular to hydrolytically stable formulations of Compound 1 having a bulk density sufficient to form tablets having a hardness in the range of about 6 kp to about 30 kp, wherein said formulations are prepared in a wet granulation process. The formulation is then converted to tablets by conventional compression techniques. In some embodiments, the tablets have a hardness in the range of about 12 kp to about 20 kp, more preferably between about 14 kp to about 18 kp. In some preferred embodiments, the tablets have a hardness of about 16 kp. This invention is further directed to tablets formed from these hydrolytically stable formulations of Compound 1.

In particular, this invention is directed to the surprising and unexpected result that the inclusion of a higher bulk density, water sequestering agent with Compound 1 in the formulation, allows for use of water in a wet granulation process notwithstanding the hydrolytic instability of Compound 1.

This invention is further directed to the discovery that the bulk density of the resulting homogenous formulation correlates to compressed tablet hardness and that control of the bulk density to between about 0.35 g/mL and about 0.65 g/mL, and preferably between about 0.35 g/mL and about 0.60 g/mL, provides for tablets having a hardness in the range of about 6 kp to about 30 kp. Such tablets also exhibit at least

75% dissolution in less than 45 minutes in an aqueous solution maintained at pH 7.4 and a temperature of 37° C.±0.5° C.

This invention is still further directed to the discovery that the tablets of this invention have surprisingly long shelf-life with minimal degradation of Compound 1 during storage under ambient conditions. Accordingly, the tablets so formed are suitable for oral delivery.

In view of the above, in one of its formulation aspects, this invention is directed to a wet granulated formulation comprising water, an effective amount of Compound 1, a sufficient amount of a water sequestering agent to inhibit decomposition of Compound 1 wherein said formulation, after drying, has a bulk density sufficient to form tablets having a hardness in the range of about 6 kp to about 30 kp.

In one embodiment, the bulk density of the dried formulation is between about 0.35 g/mL to about 0.65 g/mL and preferably between about 0.35 g/mL to about 0.60 g/mL.

In another embodiment, the higher bulk density water sequestering agent is selected from the group consisting of starch (for example, partially pregelatinized starch), magnesium sulfate, calcium chloride, silica gel, kaolin and the like. Preferably, starch is employed and, more preferably, Starch 1500 available from Colorcon, Inc., West Point, Pa., USA, is employed. In some embodiments, the starch is derived from Maize (corn). In a preferred embodiment, the pregelatinized starch is derived from Maize.

In another embodiment, the formulation further comprises one or more fillers such as microcrystalline celluloses (e.g., Avicel PH 102 (FMC Newark, Del. 19711), Emcocel 90M (JRS Pharma Patterson, N.Y. 12563), etc.) and/or one or more lubricants (e.g., magnesium stearate) and/or one or more suspending/binding agents (e.g., Plasdone K29/32 (ISP Wayne, N.J. 07470)) and/or one or more disintegrants (e.g., Sodium Starch Glycolate (JRS Pharma Rosenberg, Germany), and the like.

In another aspect, this invention is directed to a tablet comprising water, an effective amount of Compound 1, and a sufficient amount of a water sequestering agent to inhibit decomposition of Compound 1, wherein said tablet has a hardness in the range of about 6 kp to about 30 kp.

In another embodiment, the tablets of this invention exhibit at least 75% dissolution in less than 45 minutes in an aqueous solution maintained at pH 7.4 and a temperature of 37° C.±0.5° C.

In another embodiment, the tablet further comprises one or more fillers such as microcrystalline celluloses (e.g., MCC Avicel PH 102, Emcocel 90M, etc.) and/or one or more lubricants (e.g., magnesium stearate) and/or one or more suspending/binding agents (e.g., Plasdone K29/32) and/or one or more disintegrants (e.g., ExploTab), and the like.

In one of its method aspects, this invention is directed to a method for formulating Compound 1 into a formulation suitable for tablet compression which method comprises:

a) blending Compound 1 with starch and filler and optionally in the presence of one or more suspending/dispersing agents and/or more or disintegrants at an impeller speed sufficient, e.g. 155 to 405 rpm on a KG-5 High Shear Granulator, to form a homogenous mixture having a bulk density, after drying, sufficient to form tablets having a hardness of in the range of about 6 kp to about 30 kp;

b) spraying between about 15% and 40% by weight of water into the homogenous powder mixture of a) above and mixing to form enlarged granules; and

c) drying the enlarged granules produced in b) above until an LOD of between about 5% and about 11% is achieved, to provide dried granules.

The dried granules prepared in the methods above are typically between about 25 μm and about 900 μm in diameter.

In another of its method aspects, this invention further comprises milling the dried granules. In one embodiment, the dried granules are milled so that about 90 weight percent have a particle size between about 25 μm to about 900 μm in diameter.

In still another aspect, the dried, milled granules are mixed with a lubricant until homogenous, and then tabletting the resulting formulation. Suitable lubricants include stearic acid, colloidal silica and talc.

The tablets of this invention preferably comprise from about 25 mg to about 200 mg of Compound 1. More preferably, the tablets comprise between about 50 mg to about 100 mg of Compound 1 and, even more preferably, about 100 mg of Compound 1.

In another aspect, this invention provides a wet granulating process, comprising the following steps in the order shown:

a) blending a composition comprising Compound 1 and a water sequestering agent to form a blended mixture;

b) granulating the blended mixture of a) while adding water to form wet granules;

c) drying the wet granules of b) at <65° C. until an LOD of between about 5% and 11% is achieved to provide dried granules; and

d) blending a lubricant into the dried granules of c) to provide blended granules.

In another aspect, the method further comprises: (e) compressing the blended granules to form tablets.

In another aspect, this invention provides a wet granulated formulation comprising a therapeutically effective amount of Compound 1, a water sequestering agent, a lubricant, and about 5% to about 11% water. In another aspect, the formulation has a bulk density of between about 0.35 to about 0.60 g/mL. In another aspect, this invention provides a tablet formed by compressing the formulation.

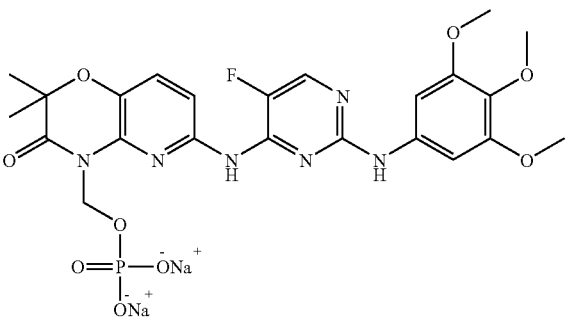
DETAILED DESCRIPTION OF THE INVENTION

The invention provides higher density, hydrolytically stable formulations of Compound 1 prepared by a wet granulation process. Such formulations inhibit degradation of Compound 1 during prolonged storage under ambient conditions.

DEFINITIONS

The term "Compound 1" refers to the following compound and hydrates thereof including its hexahydrate:

Compound 1

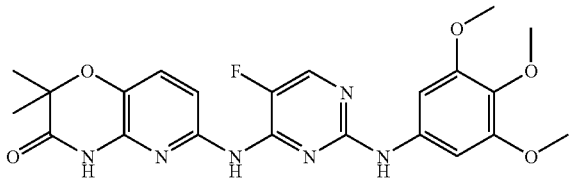


Compound 1 is sometimes referred to herein as (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt. It is understood that the disodium salt is used for exemplary purposes only and that other pharmaceutically acceptable salts such as, but not limited to, the dipotassium salt or calcium salt, or magnesium salt can be used in place thereof. Compound 1 includes any of such other salts. Compound 1 also includes hydrates thereof, including but not limited to the hexahydrate of Compound 1.

Compound 1 is disclosed in U.S. patent application Ser. No. 11/453,731, published as US 2006-0234983 A1 which is incorporated by reference in its entirety.

The term "Compound 2" refers to the following compound and hydrates thereof:

Compound 2



Compound 2 is sometimes referred to herein as 6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one.

As used herein, the term "water sequestering agent" refers to pharmaceutically acceptable agents capable of absorbing water. Examples of suitable water sequestering agents include, but are not limited to, starch, calcium chloride, silica gel, kaolin, etc.

As used herein, the term "suspending/dispersing agent" refers to a pharmaceutically acceptable compound or composition that prevents or retards the settling of solid particles of the formulation of compound 1. Examples of suitable suspending/dispersing agents include, but are not limited to, Plasdone K29/32, Plasdone S-630, hydropropyl cellulose, methylcellulose, polyvinylpyrrolidone, aluminum stearate, hydroxypropylmethylcellulose and the like.

As used herein, the term "filler" refers to any pharmaceutically acceptable inert material or composition added to a formulation to add bulk. Suitable fillers include, for example, microcrystalline cellulose.

As used herein, the term "lubricant" refers to any pharmaceutically acceptable agent which reduces surface friction, lubricates the surface of the granule, decreases tendency to build-up of static electricity, and/or reduces friability of the granules. Lubricants can also play a related role in improving the coating process, by reducing the tackiness of binders in the coating. Thus, lubricants can serve as anti-agglomeration agents and wetting agents. Examples of suitable lubricants are magnesium stearate, stearic acid, or other hydrogenated vegetable oil or triglycerides.

As used herein, the term "disintegrant" refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Examples of disintegrants include, but are not limited to, non-saccharide water soluble polymers, such as cross-linked povidine, can be added to the formulation to further enhance the rate of disintegration. Other disintegrants that can also be used include, e.g., croscarmellose sodium, sodium starch glycolate, and the like; see, e.g., Khattab (1992) J. Pharm. Pharmacol. 45:687-691.

As used herein, the term "bulk density" refers to the uncompressed, untapped powder bulk density, as measured by pouring an excess of powder sample through a funnel into a smooth metal vessel (e.g., a 500 mL volume cylinder), scraping off the excess from the heap above the rim of the vessel, measuring the remaining mass of powder and dividing the mass by the volume of the vessel.

As used herein, the term "tapped density" refers to density at constant volume. That is, a loose powdered sample (with a corresponding "bulk density") is placed in a vessel, e.g. in a graduated cylinder, and the vessel tapped on a surface, e.g. on the order of tens to hundreds of times, to compact the sample to constant volume. The density of the sample, once constant volume is reached via tapping, is the tapped density.

As used herein, the term "flow index" refers to a simple technique for the determination of powder flow characteristics.

The term "drying" and "dried" refer to a process which decreases the water content of a composition to a desired level.

The terms "compressing," "pressing," "molding" and "press molding" refer to the process of applying compressive force to a formulation (powder or granules), as within a die, to form a tablet. The terms "compressed tablet" and "pressed tablet" mean any tablet formed by such a process.

The term "tablet" is used in its common context, and refers to a solid composition made by compressing and/or molding a mixture of compositions in a form convenient for swallowing or application to any body cavity.

Formulations

Prior to tabletting, a wet granulated formulation is prepared, dried, milled and mixed, etc.

The wet granulated formulation comprises water, compound 1, and a sufficient amount of a higher bulk density water sequestering agent, such that after drying the wet formulation, the bulk density of the formulation is sufficient to provide for tablets having a hardness of between about 8 kp to about 24 kp.

The wet granulated formulation preferably comprises between about 10 to about 50 weight percent of Compound 1, about 100 to about 140 weight percent of a water sequestering agent based on the amount of Compound 1, and between about 90 to about 120 weight percent of water based on the total weight of the dry formulation prior to wet granulation.

Optional additives which can be added to the formulation include one or more of the following:

a) fillers which, when employed, preferably range between about 30 to about 45 weight percent of the dry formulation prior to wet granulation;

b) suspending/dispersing agents or binding agents which, when employed preferably range between about 2 to about 5 weight percent of the dry formulation prior to wet granulation;

c) lubricants which, when employed, range from between about 0.25 and 2.0 weight percent of the dry formulation prior to wet granulation; and

d) disintegrants which, when employed, range from between about 0.5 and 10.0 weight percent of the dry formulation prior to wet granulation;

each of which is described above.

Preferably, the wet granulated formulation comprises Compound 1, a water sequestering agent, water, filler, suspending/dispersing agent and a disintegrant.

The wet formulation can additionally and optionally include a colorant, as long as it is approved and certified by the FDA. For example, exemplary colors include allura red,

acid fuschin D, naphtalone red B, food orange 8, eosin Y, phyloxine B, erythrosine, natural red 4, carmine, to name a few.

Sweetening agents can also be added to the formulation or the outer core of the tablet to create or add to the sweetness. Saccharide fillers and binders, e.g., mannitol, lactose, and the like, can add to this effect. For example, cyclamates, saccharin, aspartame, acesulfame K (Mukherjee (1997) Food Chem. Toxicol. 35:1177-1179), or the like (Rolls (1991) Am. J. Clin. Nutr. 53:872-878), can be used. Sweeteners other than sugars have the advantage of reducing the bulk volume of the tablet (core tablet and/or coat) and not effecting the physical properties of the tablet.

Manufacturing Processes

The preferred manufacturing process of this invention for wet granulation comprises preblending all of the required formulation components except water until homogenous. In one preferred embodiment, preblending is conducted in a granulator such as a Fielder PMA 300 High Shear Granulator with 36 inch impeller diameter, and preblending comprises mixing the components together at impellor speeds ranging between about 30 to about 70 rpm for a period of between about 0.5 to about 5 minutes.

Water is then sprayed onto/into the dry composition to form the wet granulated formulation described herein. The water is preferably added at a constant rate over a period of from about 1 kg/min to about 5 kg/min with either constant mixing during addition or mixing after addition. In either event, mixing is continued until the wet granulated composition is homogenous.

The wet granulated formulation is then dried using conventional techniques to reduce water content to a predetermined level. Preferably, the water content of the dried granulated formulation is between about 5% to about 11% by weight. Drying can be conducted at various temperatures and times. One skilled in the art could readily determine the appropriate drying times based on the initial water content, the desired final water content, and the drying temperature(s) employed.

The dried granulated formulation is milled using conventional techniques and machinery. In one embodiment, the formulation is milled through an appropriate mesh screen using commercially available milling equipment such as, e.g., Quadro Comil 196S (Quadro, Millbum, N.J.).

In one embodiment, the milled, dried granulated formulation is evaluated for degree of degradation of Compound 1 to Compound 2 as well as to confirm that the bulk density of the formulation will provide for tablet hardness of between about 8 to about 24 kp upon compression. Surprisingly, it has been found that the use of water in the wet granulation process as well as elevated temperatures during the drying protocol, does not significantly alter the amount of Compound 1 in the formulation. Typically, no more than 1% by weight of Compound 1 degrades during the granulation and drying process and even more preferably no more than 0.5% by weight.

The pressing or compression of the dried, granulated and milled formulation can be accomplished using any tablet press. Many alternative means to effect this step are available, and the invention is not limited by the use of any particular equipment. In a preferred embodiment, the compression step is carried out using a rotary type tablet press. The rotary type tabletting machine has a rotary board with multiple through-holes, or dies, for forming tablets. The formulation is inserted into the die and is subsequently press-molded.

The diameter and shape of the tablet depends on the die and punches selected for the compression of the milled and mixed formulation. Tablets can be discoid, oval, oblong, round, cylindrical, triangular, and the like. The tablets may be scored to facilitate breaking. The top or lower surface can be embossed or debossed with symbols or letters.

The compression force can be selected based on the type/model of press, a desired hardness of the resulting tablets of from about 8 kp to about 24 kp as well as other attributes, such as friability, disintegration or dissolution characteristics, etc. Preferred embodiment are described in the Examples below.

Measuring Tablet Properties

Tablet hardness is a physical strength measurement of a tablet. The resistance of a tablet to chipping, abrasion, or breakage under conditions of storage, transportation, and handling before usage depends on its hardness, or "crushing strength." The tablet "crushing" or "tensile" strength is defined as the force required to break a tablet by compression in the radial direction. It is typically measured using one of the many commonly available tablet hardness testers. For example, "Stokes" and "Monsanto" hardness testers measure the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. A "Strong-Cobb" hardness tester also measures the diametrically applied force required to break a tablet, the force applied by an air pump forcing a plunger against the tablet placed on an anvil. Electrically operated hardness testers, such as the Schleuniger apparatus (also known as a "Heberlein") can be used. See also, TS-50N, Okada Seiko Co., Japan; Bi (1996) Chem. Pharm. Bull. (Tokyo) 44:2121-2127.

Tablet friability is a physical strength measurement of a tablet, and is defined as the ability of the compressed tablet to resist abrasion and attrition. It is typically measured by turning tablets in a rotating vessel and determining weight loss (see De Jong (1987) Pharm Weekbl (Sci) 9:24-28). These rotating devices are called "friabilators." The friabilator provides frictional abrasion to the tablet sample and is used to measure the resistance to abrasion or attrition of tablets. The loss of weight is measured after a fixed number of revolutions of a drum rotating at a controlled rate.

Friabilator apparatus typically use a 285 mm drum of transparent synthetic polymer with polished internal surfaces. One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection that extends from the middle of the drum to the outer wall. The drum is attached to the horizontal axis of a device that rotates at about 25 to 30 rpm. Thus, at each turn, the tablets roll or slide and fall onto the drum wall or onto each other. Many such apparatus are commonly available, e.g., the Roche type friabilator (Van Kel Industries, Inc., Edison, N.J.); a Erweka Friability Apparatus (Erweka Instruments, Milford, Conn.) (Bi (1996) supra, Chowhan (1982) J. of Pharm. Sci. 71:1371-1375), and the like.

In one exemplary protocol, the standard United States Pharmacopia (USP) protocol for measuring friability is used. Briefly, the tablets are placed in a friabilator that is a 285 mm drum, about 39 mm in depth, of transparent synthetic polymer. The tablets are "tumbled" at each turn of the drum by a curved projection that extends from the middle of the drum. The drum is rotated for about four minutes at about 25 rpm, resulting in a total of 100 rotations. A minimum of about 20 tablets are used in any test, unless the tablets weigh over 650 mg, in which case only 10 tablets are used. After the allotted time, the tablets are removed from the friabilator, and, with the aid of air pressure or a brush, adhering particles and dust are removed, and remaining tablets are accurately weighed. Percent loss of weight is calculated.

Tablet dissolution is measured by the amount of time for 75% of the tablet to dissolve in an aqueous solution buffered to pH 7.4 and maintained at 37° C.±0.5° C. and paddle mixed at an rpm of 75.

Further examples of tablet formation are provided in U.S. Pat. No. 6,669,956 which is incorporated herein by reference in its entirety.

EXAMPLES

The invention is further understood by reference to the following examples, which are intended to be purely exem-

plary of the invention. The present invention is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only. Any methods that are functionally equivalent are within the scope of the invention. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications fall within the scope of the appended claims.

In the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

mL=Milliliter
g=Gram
mg=Milligram
rpm=revolutions per minute
min=Minute
mm=Millimeter
v/v=volume/volume
° C.=degree Celsius
LOD=lost on drying
kp=kilopond (=1 kilogram (kg) or 9.807 Newtons of force)
API=active pharmaceutical ingredient

Materials and Equipment

Compound 1
Microcrystalline Cellulose Avicel 102 (Patheon)
Emcocel 90M, JRS Pharma E9B4B11X
Starch 1500, Colorcon, (Patheon)
Plasdone S-630, ISP
Plasdone K29/32, ISP (Patheon)
Explotab JRS Pharma (Patheon)
Magnesium Stearate, Mallinkrodt
Punch & Die for 500 mg tablet, 0.3510"×0.6299", Oval Shape
Balance, AX105, Mettler-Toledo Inc.
Balance, PG3001-S, Mettler-Toledo Inc.
Tablet Friabilator (USP), Pharma Alliance
Mini Blend V-Blender, Globe Pharma
USA Standard Testing Sieves
MiniGlatt Fluid Bed Dryer, Type 3, Glatt
Tablet Hardness Tester, Holland C40 Tablet Hardness Tester, Engineering Systems
Differential Scanning Calorimeter, DSC Q100 by TA Instruments
Laboratory Humidity Chamber Mod. LH-1.5, Associated Environmental Systems
X-Ray Powder Diffraction, Miniflex Tabletop XRD System by Rigaku/MSC, The Woodlands, Tex.
Stokes B-2 Rotary Tablet Press
HPLC System, Waters with Photodiode Array Detector
Dissolution Tester, Sotax Dissolution with Rainbow Monitor System
Moisture Analyzer HB43, Mettler-Toledo Inc.
Flodex Powder Flow Tester, Hanson Research Corp.
High Shear Granulator, Mod. KG-5, Key International, Inc.

Example 1

Preparation of Final Blend

A 125 g batch of Compound 1 granules were prepared by mixing Compound 1 with all the excipients except magnesium stearate (listed in Table 1) on a paper tray using a spatula, granulated with approximately 130 g of water. Granules were dried in the fluid bed at 60° C. and collected at 7.3% and 6.5% LOD. They were then milled, and blended with 2% magnesium stearate for 2 minutes to make the final blend. The formulation is shown in Table 1. The final blend was characterized and pressed into tablets. The tablets were tested for potency and impurities, hardness and dissolution. Example 2 shows a final blend composition (Table 2) using a KG-5 High Shear Granulator.

TABLE 1

Excipient	wt (g)
Compound 1	32.5
Avicel PH102	38.75
Starch 1500	40
Plasdone K29/32	3.75
Explotab	7.5
Magnesium Stearate	2.5
Total	125

Example 2

Preparation of Final Blend Using a KG-5 High Shear Granulator

TABLE 2

Excipient	wt (g)
Compound 1	130
MCC Avicel PH102	157.5
Starch 1500	160
Plasdone K29/32	15
Explotab	30
Magnesium Stearate	7.5
Total	500

Example 3

Preparation of Compound 1 Powder Blend

Three 500 g batches of Compound 1 powder blends (see Table 3) were prepared according to the following method. A KG-5 High Shear Granulator with an 8-inch impeller diameter was used to preblend all ingredients (except magnesium stearate) at low (155 rpm), medium (405 rpm), or high (600 rpm) impeller speeds with the chopper speed of 1200 rpm for 2 minutes. Water was added at a rate of 30 to 31.5 g/min to the powder mix. After the full amount of water was added, the mixture was blended for an additional 2 minutes. The wet granules were dried with the MiniGlatt Fluid Bed Dryer at 60° C. to targeted LODs and the granule texture, size, shape, stickiness, etc visually inspected. Drying at various temperatures and times are evaluated also. The granules were milled through CoMill U3 with 0 32R mesh screen (0.0331 inch diameter holes), 1.5% magnesium stearate was added and mixed for 2 minutes in the V-blender to make the final blends. The final blends were checked for degradation by HPLC, and physical properties determined such as, Bulk Density, Tapped Density, Carr's Index, Hausner Ratio and Flow Index by Flodex. The final blends were compressed into 500 mg tablets using Stokes B-2 Rotary Press with 0.3071×0.6102 inches modified oval punches. The tablets were compressed with the same pressure settings to obtain maximum/achievable tablet hardness.

TABLE 3

Excipient	wt (g)
Compound 1	130
MCC Avicel PH102	157.5
Starch 1500	160
Plasdone K29/32	15
Explotab	30
Magnesium Stearate	7.5
Total	500

Carr's Index is a measure of compressibility of powder and defined as percent of (Tapped Density−Bulk Density)/Tapped Density. The higher the index, the more compressible of the powder and the poorer the flow. An index is 5 to 15% indicates excellent to good flowability. The Hausner Ratio is the ratio of Tapped Density to Bulk Density and is an assessment of interparticulate friction. A ratio of <1.6 is an indication of acceptable friction, in other words good powder flow. The maximum achievable hardness is defined as the hardness achieved with the maximum compression force.

Example 4

Physical Properties of Final Blend

Compound 1 (as the hexahydrate) was granulated with the excipients (except magnesium stearate) in Table 4. The physical properties of the final blend made by granulating Compound 1 with all the excipients together and drying to 6.5% LOD were measured and are shown in Table 5.

TABLE 4

Excipient	wt (g)
Compound 1	32.5
MCC Avicel PH102	38.75
Starch 1500	40
Plasdone K29/32	3.75
Explotab	7.5
Magnesium Stearate	2.5
Total	125

TABLE 5

Bulk Density	0.374 g/mL
Tapped Density	0.420 g/mL
Carr's Index	11.0%
Hausner Ratio	1.12
Flow Index	16 mm

The Carr's Index of 15% and a flow index of 16 mm indicate an excellent powder flow of the final blend.

Example 5

Maximum Achievable Hardness of Tablets

Tablets from final blends prepared as described in Example 4 with 7.27% and 6.47% LOD and were compressed and the hardness determined. The results are provided in Table 6. The tablet hardness was the maximum that was achievable. As demonstrated, tablets with hardness of 27.9 to 33.8 kp were obtained. All the tablets from these final blends appeared off-white and highly homogeneous. The final blend with 6.47% was compressed to tablets with hardness of 20 kp and 30 kp. The tablets displayed >75% dissolution after 30 minutes, indicating a large tolerance with respect to the hardness of tablets.

TABLE 6

LOD of Final Blend = 7.27%			LOD of Final Blend = 6.47%		
Weight, mg	Hardness, kp	Thickness, mm	Weight, mg	Hardness, kp	Thickness, mm
500	27.9	4.98	505	33.8	5.06
504	29.8	5.05	506	32.2	5.08
501	29.1	5.04	505	33.8	5.08

Example 6

Stability of Compound 1 in Tablets

Tablets from Example 5 were stored under intensified shelf-life conditions (one month at 40° C. and 75% Relative Humidity) and analyzed for purity and potency by HPLC. Analysis results for tablets after one month at the aforementioned showed a purity of 98.8-99.1%.

Example 7

Dependence of Tablet Hardness on Density of Blend

Select batches of granules which were produced by methods described in Example 3, were further subjected to the various granulation parameters shown in Table 7. The impeller speed was varied and it was observed that low impeller speeds lead to less dense granules. In addition, the amount of water sprayed during the process was evaluated and it was found that less water sprayed may also help to lower the density of granules.

TABLE 7

	Batch		
	A	B	C
Batch Size, g	500	500	450
Impeller Speed, rpm	405	600	155
Chopper Speed, rpm	2000	2000	1200
Water added g/min	30	30	31.5
Water consumed, g	250	260	185
LOD of wet granules	37.1%	38.9%	33.7%
LOD of dry granules	6.5%	6.0%	6.6%
Bulk Density, g/mL	0.570	0.621	0.505
Tapped Density, g/mL	0.632	0.674	0.583
Hausner Ratio	1.11	1.09	1.15
Carr's Index	9.81	7.86	13.4
Flow Index	14 mm	14 mm	14 mm

* Batch C is a combination of three independent batches. Experimental procedures for Batch A, B, C are the same except the Impeller speed, chopper speed, rate and amount of water added.

All the granules possess excellent flow properties as measured by Hauser ratio, Carr's index and flow index. The LOD of dry granules, 6.0 to 6.6%, is close to 7.1% as in the starting blend. These blends appeared ideal for tablet compression.

Tablets were compressed from these blends after blending with magnesium stearate at the maximum compression force. Results are summarized in Table 8. The less dense the blend, the harder the tablets. The blend with density of 0.65 g/mL resulted in tablets with the maximum hardness of 5-8 kp.

TABLE 8

Tablet wt, mg	Hardness, kp	Thickness, mm
Maximum Tablet Hardness for Batch A: Bulk Density 0.570 g/Ml		
517	20.8	5.09
521	20.2	5.18
516	19.2	5.21
Maximum Tablet Hardness for Batch B: Bulk Density 0.621 g/mL		
501	17.3	4.91
502	16.3	4.93
502	15.0	4.94
Maximum Tablet Hardness for Batch C: Bulk Density 0.505 g/mL		
507	35.9	5.01
502	35.4	4.99
500	33.7	4.98

Example 8

Moisture Content (LOD) Vs. Hardness of Tablets with Density of the Blend <0.55 g/mL

The granules from Batch A (Example 7) were dried at 50° C., 60° C. and 70° C. to LOD of 6.4 to 6.8%. The dried granules were assayed by HPLC. The purity/impurity profiles remained the same for the three drying conditions. Compared to API, there was 0.15% decrease in purity and the same amount of increase in Compound 2. The tablets compressed from Batch A were dried and analyzed via HPLC and gave similar results to the granules. The dissolution of the tablets was >75% after 30 min.

Example 9

Moisture Content (LOD) Vs. Hardness

Batch C (Example 7) was further dried in 6×65 g lots (Labeled C-1 to C-6) to LOD of 4.7, 5.6, 6.7, 7.6, 8.7 and 9.3%. All the dried granules were milled through CoMil with #25 mesh screen, and mixed with 1.5% magnesium stearate for 2 minutes. The physical properties of the final blends are summarized in Table 9.

TABLE 9

	C-1	C-2	C-3	C-4	C-5	C-6
LOD, %	4.70	5.58	7.55	6.74	8.74	9.33
Sample Weight, g	51.2	50.1	48.9	51.1	48.3	49.8
Bulk Density, g/mL	0.517	0.506	0.499	0.511	0.503	0.507
Tapped Density, g/mL	0.595	0.589	0.579	0.581	0.574	0.586
Carr's Index	13.1	14.1	13.8	12.1	12.4	13.5
Hausner Ratio	1.15	1.16	1.16	1.14	1.14	1.16

The final blends C-1-C-6 from Table 9 were compressed separately into 500 mg tablets under the same maximum compression force. LOD of the final blends, weight, hardness and thickness of the tablets are provided in Table 10.

TABLE 10

	wt, mg	Hardness, kp	Thickness, mm
Tablet C-1	477	29.2	4.85
LOD = 4.70%	513	32.5	5.08
	514	34.4	5.09
Tablet C-2	516	35.2	5.04
LOD = 5.58%	511	31.3	5.08
	500	31.9	4.99
Tablet C-4	507	35.9	5.01
LOD = 6.74%	502	35.4	4.99
	500	33.7	4.98
Tablet C-3	502	33.0	4.94
LOD = 7.55%	500	33.0	4.92
	503	32.7	4.95
Tablet C-5	502	29.5	4.93
LOD = 8.74%	500	29.0	4.94
	503	26.0	4.94
Tablet C-6	506	26.9	4.97
LOD = 9.33%	505	26.4	4.97
	505	27.0	4.99

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entireties.

Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

What is claimed is:

1. A formulation comprising water, (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt and a sufficient amount of a water sequestering agent to inhibit decomposition of (6-(5-fluoro-2-(3,4,5-trimethoxyphenyl-amino) pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl) methyl phosphate disodium salt during granulation, tablet formation and/or storage, wherein said formulation, after drying, has a bulk density sufficient to form tablets having a hardness in the range of about 6 kp to about 30 kp.

2. The formulation of claim **1**, wherein after drying the formulation has a bulk density of between about 0.35 to about 0.65 g/mL.

3. The formulation of claim **1**, wherein the water sequestering agent is selected from the group consisting of starch, magnesium sulfate, calcium chloride, silica gel, and kaolin.

4. The formulation of claim **3**, wherein the water sequestering agent is starch.

5. The formulation of claim **4**, wherein the starch is partially pregelatinized.

6. The formulation of claim **5**, wherein the starch is derived from Maize.

7. The formulation of claim **1** which further comprises at least one of a filler, a lubricant, a suspending/dispersing agent, a binding agent, and a disintegrant.

8. A tablet comprising water, a therapeutically effective amount of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)

pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt and a sufficient amount of a water sequestering agent to inhibit decomposition of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino) pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt, wherein said tablet has a hardness in the range of about 6 kp to about 30 kp.

9. The tablet of claim **8**, wherein said tablet exhibits at least 75% dissolution in less than 45 minutes in an aqueous solution maintained at pH 7.4, a temperature of 37° C.+0.5° C., and a paddle speed of 75 rpm.

10. The tablet of claim **8** which further comprises at least one of a filler, a lubricant, a suspending/dispersing agent, a binding agent, and a disintegrant.

11. The tablet of any of claim **8**, **9** or **10**, wherein the tablet comprises from greater than 25 mg to about 200 mg of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino) pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt.

12. The tablet of claim **11**, wherein the tablet comprises about 50 mg to about 100 mg of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino) pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt.

13. The tablet of claim **12**, wherein the tablet comprises about 100 mg of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino) pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt.

14. A formulation comprising a therapeutically effective amount of Compound 1, a water sequestering agent, a lubricant, and about 5% to about 11% water, wherein the water sequestering agent is present in an amount sufficient to inhibit decomposition of Compound 1.

15. The formulation of claim **14**, wherein the formulation has a bulk density of between about 0.35 to about 0.65 g/mL.

16. A tablet formed by compressing the wet granulated formulation of claim **14**.

* * * * *

EXHIBIT C

US008652492B2

(12) **United States Patent**
Sun et al.

(10) **Patent No.: US 8,652,492 B2**
(45) **Date of Patent: *Feb. 18, 2014**

(54) **WET GRANULATION USING A WATER SEQUESTERING AGENT**

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Related U.S. Application Data

(60) Continuation of application No. 13/559,097, filed on Jul. 26, 2012, now Pat. No. 8,372,415, which is a division of application No. 12/266,337, filed on Nov. 6, 2008, now Pat. No. 8,263,122.

(60) Provisional application No. 60/986,237, filed on Nov. 7, 2007.

(51) **Int. Cl.**
A61K 9/00 (2006.01)

(52) **U.S. Cl.**
USPC **424/400**

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are tablets comprising hydrolytically stable formulations of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt (Compound 1) prepared by a wet granulation process.

9 Claims, No Drawings

WET GRANULATION USING A WATER SEQUESTERING AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/559,097, filed Jul. 26, 2012, which is a divisional of U.S. application Ser. No. 12/266,337, filed Nov. 6, 2008, which claims benefit under 35 U.S.C. §119(e) to application Ser. No. 60/986,237, filed Nov. 7, 2007, the contents of which are incorporated herein by reference in their entirety.

I. INTRODUCTION

1. Field of the Invention

This invention relates to pharmaceutical/formulation chemistry. The invention is understood to apply generally to formulations of hydrolytically unstable compounds. As a preferred embodiment, provided herein are higher density, hydrolytically stable formulations of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino) pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt (Compound 1) prepared by a wet granulation process. Such formulations inhibit degradation of Compound 1 during prolonged storage under ambient conditions. The formulations are useful for treating a variety of diseases including, but not limited to, lymphoma, immune (idiopathic) thrombocytopenia purpura (ITP), and rheumatoid arthritis (RA).

2. State of the Art

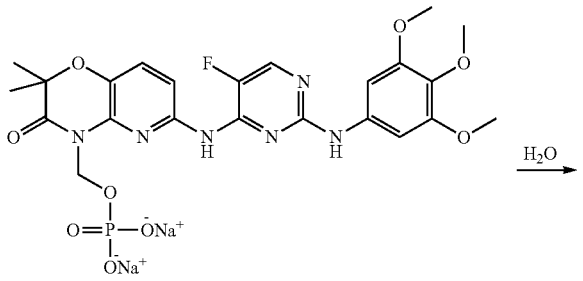
Compound 1 is currently in clinical studies for the treatment of a variety of diseases such as lymphoma, ITP and RA. Dosing is currently done with orally delivered tablets. Two sets of tablets used contain relatively high concentrations of Compound 1, i.e., 50 mg and 100 mg of active.

Compound 1, as synthesized, forms cotton like fluffy agglomerates with a very low bulk density (~0.15-0.30 g/mL). This characteristic confers poor powder flow and makes direct compression to tablets of the active impractical. Poor powder flow also results in a wide weight variation within the final product owing to variable fill of tablet dies, etc. Accordingly, it is desirable to formulate Compound 1 with higher density excipients such as fillers, binders, disintegrants, etc. which increase the bulk density and render the flow property adequate for compression into tablets.

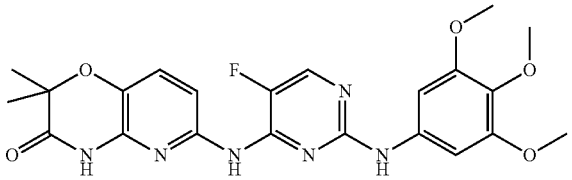
Granulation is a process well known in the pharmaceutical industry, involving the preparation of aggregates ("granules") of fine particles of materials. Such granules are often compacted to form tablets. Formulations of pharmaceutical powders are granulated for a variety of reasons falling into two main classes: processing and formulation. Processing reasons are exemplified by the need for densification and aggregation. A dense, granular material will flow more evenly and fill dies on high speed tablet machines better and with greater consistency than a simple mixture.

One method of making granules is so called "wet granulation." In its simplest form, wet granulation involves the addition of a granulating fluid, commonly water, functioning as a granulating liquid, to a stirred powder comprising the materials to be granulated. The granulating liquid can be used alone or as a solvent containing a binder (also referred to as a "dissolved adhesive") which is used to ensure particle adhesion once the granule is dry. If the drying and subsequent handling is done with care, the aggregates will retain their integrity, giving a material which is both denser and more free flowing than the original material. Wet granulation has also been carried out with organic solvents or water-organic solvent mixtures, but organic solvents can present fire or toxicity hazards.

Wet granulation adds a significant degree of difficulty especially where the active agent is sensitive to water or heat. This invention is contemplated for hydrolytically unstable compounds generally. Compound 1, including its hexahydrate, is water sensitive and undergoes decomposition according to the following reaction scheme:



Compound 1



Compound 2

Compound 1 is a prodrug of Compound 2. It is preferable, then, that any wet granulation process employing water be done in a manner where little or no degradation of Compound 1 occurs either during the granulation, tablet formation, or storage so as to ensure that the proper systemic levels of Compound 2 are achieved.

In addition, it is preferable that the tablets formed be of sufficient hardness that they can be hand manipulated without breakage but disintegrate rapidly upon administration.

II. SUMMARY OF THE INVENTION

This invention is generally directed to hydrolytically stable formulations of hydrolytically unstable compounds, in particular to hydrolytically stable formulations of Compound 1 having a bulk density sufficient to form tablets having a hardness in the range of about 6 kp to about 30 kp, wherein said formulations are prepared in a wet granulation process. The formulation is then converted to tablets by conventional compression techniques. In some embodiments, the tablets have a hardness in the range of about 12 kp to about 20 kp, more preferably between about 14 kp to about 18 kp. In some preferred embodiments, the tablets have a hardness of about 16 kp. This invention is further directed to tablets formed from these hydrolytically stable formulations of Compound 1.

In particular, this invention is directed to the surprising and unexpected result that the inclusion of a higher bulk density, water sequestering agent with Compound 1 in the formulation, allows for use of water in a wet granulation process notwithstanding the hydrolytic instability of Compound 1.

This invention is further directed to the discovery that the bulk density of the resulting homogenous formulation correlates to compressed tablet hardness and that control of the bulk density to between about 0.35 g/mL and about 0.65

g/mL, and preferably between about 0.35 g/mL and about 0.60 g/mL, provides for tablets having a hardness in the range of about 6 kp to about 30 kp. Such tablets also exhibit at least 75% dissolution in less than 45 minutes in an aqueous solution maintained at pH 7.4 and a temperature of 37° C.±0.5° C.

This invention is still further directed to the discovery that the tablets of this invention have surprisingly long shelf-life with minimal degradation of Compound 1 during storage under ambient conditions. Accordingly, the tablets so formed are suitable for oral delivery.

In view of the above, in one of its formulation aspects, this invention is directed to a wet granulated formulation comprising water, an effective amount of Compound 1, a sufficient amount of a water sequestering agent to inhibit decomposition of Compound 1 wherein said formulation, after drying, has a bulk density sufficient to form tablets having a hardness in the range of about 6 kp to about 30 kp.

In one embodiment, the bulk density of the dried formulation is between about 0.35 g/mL to about 0.65 g/mL and preferably between about 0.35 g/mL to about 0.60 g/mL.

In another embodiment, the higher bulk density water sequestering agent is selected from the group consisting of starch (for example, partially pregelatinized starch), magnesium sulfate, calcium chloride, silica gel, kaolin and the like. Preferably, starch is employed and, more preferably, Starch 1500 available from Colorcon, Inc., West Point, Pa., USA, is employed. In some embodiments, the starch is derived from Maize (corn). In a preferred embodiment, the pregelatinized starch is derived from Maize.

In another embodiment, the formulation further comprises one or more fillers such as microcrystalline celluloses (e.g., Avicel PH 102 (FMC Newark, Del. 19711), Emcocel 90M (JRS Pharma Patterson, N.Y. 12563), etc.) and/or one or more lubricants (e.g., magnesium stearate) and/or one or more suspending/binding agents (e.g., Plasdone K29/32 (ISP Wayne, N.J. 07470)) and/or one or more disintegrants (e.g., Sodium Starch Glycolate (JRS Pharma Rosenberg, Germany), and the like.

In another aspect, this invention is directed to a tablet comprising water, an effective amount of Compound 1, and a sufficient amount of a water sequestering agent to inhibit decomposition of Compound 1, wherein said tablet has a hardness in the range of about 6 kp to about 30 kp.

In another embodiment, the tablets of this invention exhibit at least 75% dissolution in less than 45 minutes in an aqueous solution maintained at pH 7.4 and a temperature of 37° C.±0.5° C.

In another embodiment, the tablet further comprises one or more fillers such as microcrystalline celluloses (e.g., MCC Avicel PH 102, Emcocel 90M, etc.) and/or one or more lubricants (e.g., magnesium stearate) and/or one or more suspending/binding agents (e.g., Plasdone K29/32) and/or one or more disintegrants (e.g., ExploTab), and the like.

In one of its method aspects, this invention is directed to a method for formulating Compound 1 into a formulation suitable for tablet compression which method comprises:

a) blending Compound 1 with starch and filler and optionally in the presence of one or more suspending/dispersing agents and/or more or disintegrants at an impeller speed sufficient, e.g. 155 to 405 rpm on a KG-5 High Shear Granulator, to form a homogenous mixture having a bulk density, after drying, sufficient to form tablets having a hardness of in the range of about 6 kp to about 30 kp;

b) spraying between about 15% and 40% by weight of water into the homogenous powder mixture of a) above and mixing to form enlarged granules; and

c) drying the enlarged granules produced in b) above until an LOD of between about 5% and about 11% is achieved, to provide dried granules.

The dried granules prepared in the methods above are typically between about 25 μm and about 900 μm in diameter.

In another of its method aspects, this invention further comprises milling the dried granules. In one embodiment, the dried granules are milled so that about 90 weight percent have a particle size between about 25 μm to about 900 μm in diameter.

In still another aspect, the dried, milled granules are mixed with a lubricant until homogenous, and then tabletting the resulting formulation. Suitable lubricants include stearic acid, colloidal silica and talc.

The tablets of this invention preferably comprise from about 25 mg to about 200 mg of Compound 1. More preferably, the tablets comprise between about 50 mg to about 100 mg of Compound 1 and, even more preferably, about 100 mg of Compound 1.

In another aspect, this invention provides a wet granulating process, comprising the following steps in the order shown:

a) blending a composition comprising Compound 1 and a water sequestering agent to form a blended mixture;

b) granulating the blended mixture of a) while adding water to form wet granules;

c) drying the wet granules of b) at <65° C. until an LOD of between about 5% and 11% is achieved to provide dried granules; and

d) blending a lubricant into the dried granules of c) to provide blended granules.

In another aspect, the method further comprises: (e) compressing the blended granules to form tablets.

In another aspect, this invention provides a wet granulated formulation comprising a therapeutically effective amount of Compound 1, a water sequestering agent, a lubricant, and about 5% to about 11% water. In another aspect, the formulation has a bulk density of between about 0.35 to about 0.60 g/mL. In another aspect, this invention provides a tablet formed by compressing the formulation.

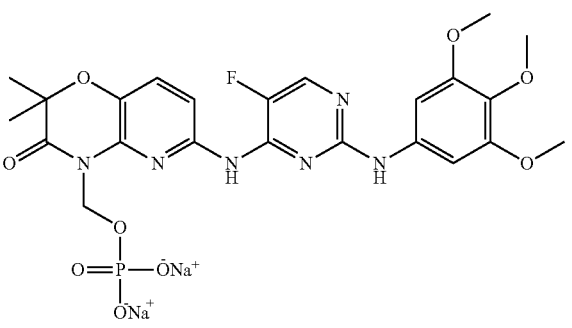
III. DETAILED DESCRIPTION OF THE INVENTION

The invention provides higher density, hydrolytically stable formulations of Compound 1 prepared by a wet granulation process. Such formulations inhibit degradation of Compound 1 during prolonged storage under ambient conditions.

Definitions

The term "Compound 1" refers to the following compound and hydrates thereof including its hexahydrate:

Compound 1

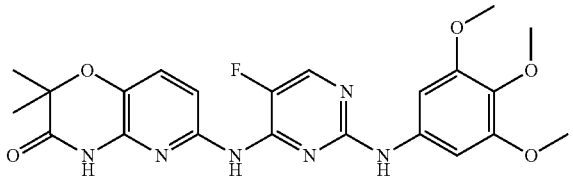


Compound 1 is sometimes referred to herein as (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt. It is understood that the disodium salt is used for exemplary purposes only and that other pharmaceutically acceptable salts such as, but not limited to, the dipotassium salt or calcium salt, or magnesium salt can be used in place thereof. Compound 1 includes any of such other salts. Compound 1 also includes hydrates thereof, including but not limited to the hexahydrate of Compound 1.

Compound 1 is disclosed in U.S. patent application Ser. No. 11/453,731, published as US 2006-0234983 A1 which is incorporated by reference in its entirety.

The term "Compound 2" refers to the following compound and hydrates thereof:

Compound 2



Compound 2 is sometimes referred to herein as 6-(5-fluoro-2-(3,4,5-trimethoxyphenyl amino)pyrimidin-4-ylamino)-2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3 (4H)-one.

As used herein, the term "water sequestering agent" refers to pharmaceutically acceptable agents capable of absorbing water. Examples of suitable water sequestering agents include, but are not limited to, starch, calcium chloride, silica gel, kaolin, etc.

As used herein, the term "suspending/dispersing agent" refers to a pharmaceutically acceptable compound or composition that prevents or retards the settling of solid particles of the formulation of compound 1. Examples of suitable suspending/dispersing agents include, but are not limited to, Plasdone K29/32, Plasdone S-630, hydropropyl cellulose, methylcellulose, polyvinylpyrrolidone, aluminum stearate, hdroxypropylmethylcellulose and the like.

As used herein, the term "filler" refers to any pharmaceutically acceptable inert material or composition added to a formulation to add bulk. Suitable fillers include, for example, microcrystal line cellulose.

As used herein, the term "lubricant" refers to any pharmaceutically acceptable agent which reduces surface friction, lubricates the surface of the granule, decreases tendency to build-up of static electricity, and/or reduces friability of the granules. Lubricants can also play a related role in improving the coating process, by reducing the tackiness of binders in the coating. Thus, lubricants can serve as anti-agglomeration agents and wetting agents. Examples of suitable lubricants are magnesium stearate, stearic acid, or other hydrogenated vegetable oil or triglycerides.

As used herein, the term "disintegrant" refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Examples of disintegrants include, but are not limited to, non-saccharide water soluble polymers, such as cross-linked povidine, can be added to the formulation to further enhance the rate of disintegration. Other disintegrants that can also be used include, e.g., croscarmellose sodium, sodium starch glycolate, and the like; see, e.g., Khattab (1992) J. Pharm. Pharmacol. 45:687-691.

As used herein, the term "bulk density" refers to the uncompressed, untapped powder bulk density, as measured by pouring an excess of powder sample through a funnel into a smooth metal vessel (e.g., a 500 mL volume cylinder), scraping off the excess from the heap above the rim of the vessel, measuring the remaining mass of powder and dividing the mass by the volume of the vessel.

As used herein, the term "tapped density" refers to density at constant volume. That is, a loose powdered sample (with a corresponding "bulk density") is placed in a vessel, e.g. in a graduated cylinder, and the vessel tapped on a surface, e.g. on the order of tens to hundreds of times, to compact the sample to constant volume. The density of the sample, once constant volume is reached via tapping, is the tapped density.

As used herein, the term "flow index" refers to a simple technique for the determination of powder flow characteristics.

The term "drying" and "dried" refer to a process which decreases the water content of a composition to a desired level.

The terms "compressing," "pressing," "molding" and "press molding" refer to the process of applying compressive force to a formulation (powder or granules), as within a die, to form a tablet. The terms "compressed tablet" and "pressed tablet" mean any tablet formed by such a process.

The term "tablet" is used in its common context, and refers to a solid composition made by compressing and/or molding a mixture of compositions in a form convenient for swallowing or application to any body cavity.

Formulations

Prior to tabletting, a wet granulated formulation is prepared, dried, milled and mixed, etc.

The wet granulated formulation comprises water, compound 1, and a sufficient amount of a higher bulk density water sequestering agent, such that after drying the wet formulation, the bulk density of the formulation is sufficient to provide for tablets having a hardness of between about 8 kp to about 24 kp.

The wet granulated formulation preferably comprises between about 10 to about 50 weight percent of Compound 1, about 100 to about 140 weight percent of a water sequestering agent based on the amount of Compound 1, and between about 90 to about 120 weight percent of water based on the total weight of the dry formulation prior to wet granulation.

Optional additives which can be added to the formulation include one or more of the following:

a) fillers which, when employed, preferably range between about 30 to about 45 weight percent of the dry formulation prior to wet granulation;

b) suspending/dispersing agents or binding agents which, when employed preferably range between about 2 to about 5 weight percent of the dry formulation prior to wet granulation;

c) lubricants which, when employed, range from between about 0.25 and 2.0 weight percent of the dry formulation prior to wet granulation; and

d) disintegrants which, when employed, range from between about 0.5 and 10.0 weight percent of the dry formulation prior to wet granulation;

each of which is described above.

Preferably, the wet granulated formulation comprises Compound 1, a water sequestering agent, water, filler, suspending/dispersing agent and a disintegrant.

The wet formulation can additionally and optionally include a colorant, as long as it is approved and certified by the FDA. For example, exemplary colors include allura red,

acid fuschin D, naphtalone red B, food orange 8, eosin Y, phyloxine B, erythrosine, natural red 4, carmine, to name a few.

Sweetening agents can also be added to the formulation or the outer core of the tablet to create or add to the sweetness. Saccharide fillers and binders, e.g., mannitol, lactose, and the like, can add to this effect. For example, cyclamates, saccharin, aspartame, acesulfame K (Mukherjee (1997) Food Chem. Toxicol. 35:1177-1179), or the like (Rolls (1991) Am. J. Clin. Nutr. 53:872-878), can be used. Sweeteners other than sugars have the advantage of reducing the bulk volume of the tablet (core tablet and/or coat) and not effecting the physical properties of the tablet.

Manufacturing Processes

The preferred manufacturing process of this invention for wet granulation comprises preblending all of the required formulation components except water until homogenous. In one preferred embodiment, preblending is conducted in a granulator such as a Fielder PMA 300 High Shear Granulator with 36 inch impeller diameter, and preblending comprises mixing the components together at impellor speeds ranging between about 30 to about 70 rpm for a period of between about 0.5 to about 5 minutes.

Water is then sprayed onto/into the dry composition to form the wet granulated formulation described herein. The water is preferably added at a constant rate over a period of from about 1 kg/min to about 5 kg/min with either constant mixing during addition or mixing after addition. In either event, mixing is continued until the wet granulated composition is homogenous.

The wet granulated formulation is then dried using conventional techniques to reduce water content to a predetermined level. Preferably, the water content of the dried granulated formulation is between about 5% to about 11% by weight. Drying can be conducted at various temperatures and times. One skilled in the art could readily determine the appropriate drying times based on the initial water content, the desired final water content, and the drying temperature(s) employed.

The dried granulated formulation is milled using conventional techniques and machinery. In one embodiment, the formulation is milled through an appropriate mesh screen using commercially available milling equipment such as, e.g., Quadro Comil 196S (Quadro, Millbum, N.J.).

In one embodiment, the milled, dried granulated formulation is evaluated for degree of degradation of Compound 1 to Compound 2 as well as to confirm that the bulk density of the formulation will provide for tablet hardness of between about 8 to about 24 kp upon compression. Surprisingly, it has been found that the use of water in the wet granulation process as well as elevated temperatures during the drying protocol, does not significantly alter the amount of Compound 1 in the formulation. Typically, no more than 1% by weight of Compound 1 degrades during the granulation and drying process and even more preferably no more than 0.5% by weight.

The pressing or compression of the dried, granulated and milled formulation can be accomplished using any tablet press. Many alternative means to effect this step are available, and the invention is not limited by the use of any particular equipment. In a preferred embodiment, the compression step is carried out using a rotary type tablet press. The rotary type tabletting machine has a rotary board with multiple through-holes, or dies, for forming tablets. The formulation is inserted into the die and is subsequently press-molded.

The diameter and shape of the tablet depends on the die and punches selected for the compression of the milled and mixed formulation. Tablets can be discoid, oval, oblong, round, cylindrical, triangular, and the like. The tablets may be scored to facilitate breaking. The top or lower surface can be embossed or debossed with symbols or letters.

The compression force can be selected based on the type/model of press, a desired hardness of the resulting tablets of from about 8 kp to about 24 kp as well as other attributes, such as friability, disintegration or dissolution characteristics, etc. Preferred embodiment are described in the Examples below.

Measuring Tablet Properties

Tablet hardness is a physical strength measurement of a tablet. The resistance of a tablet to chipping, abrasion, or breakage under conditions of storage, transportation, and handling before usage depends on its hardness, or "crushing strength." The tablet "crushing" or "tensile" strength is defined as the force required to break a tablet by compression in the radial direction. It is typically measured using one of the many commonly available tablet hardness testers. For example, "Stokes" and "Monsanto" hardness testers measure the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. A "Strong-Cobb" hardness tester also measures the diametrically applied force required to break a tablet, the force applied by an air pump forcing a plunger against the tablet placed on an anvil. Electrically operated hardness testers, such as the Schleuniger apparatus (also known as a "Heberlein") can be used. See also, TS-50N, Okada Seiko Co., Japan; Bi (1996) Chem. Pharm. Bull. (Tokyo) 44:2121-2127.

Tablet friability is a physical strength measurement of a tablet, and is defined as the ability of the compressed tablet to resist abrasion and attrition. It is typically measured by turning tablets in a rotating vessel and determining weight loss (see De Jong (1987) Pharm Weekbl (Sci) 9:24-28). These rotating devices are called "friabilators." The friabilator provides frictional abrasion to the tablet sample and is used to measure the resistance to abrasion or attrition of tablets. The loss of weight is measured after a fixed number of revolutions of a drum rotating at a controlled rate.

Friabilator apparatus typically use a 285 mm drum of transparent synthetic polymer with polished internal surfaces. One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection that extends from the middle of the drum to the outer wall. The drum is attached to the horizontal axis of a device that rotates at about 25 to 30 rpm. Thus, at each turn, the tablets roll or slide and fall onto the drum wall or onto each other. Many such apparatus are commonly available, e.g., the Roche type friabilator (Van Kel Industries, Inc., Edison, N.J.); a Erweka Friability Apparatus (Erweka Instruments, Milford, Conn.) (Bi (1996) supra, Chowhan (1982) J. of Pharm. Sci. 71:1371-1375), and the like.

In one exemplary protocol, the standard United States Pharmacopia (USP) protocol for measuring friability is used. Briefly, the tablets are placed in a friabilator that is a 285 mm drum, about 39 mm in depth, of transparent synthetic polymer. The tablets are "tumbled" at each turn of the drum by a curved projection that extends from the middle of the drum. The drum is rotated for about four minutes at about 25 rpm, resulting in a total of 100 rotations. A minimum of about 20 tablets are used in any test, unless the tablets weigh over 650 mg, in which case only 10 tablets are used. After the allotted time, the tablets are removed from the friabilator, and, with the aid of air pressure or a brush, adhering particles and dust are removed, and remaining tablets are accurately weighed. Percent loss of weight is calculated.

Tablet dissolution is measured by the amount of time for 75% of the tablet to dissolve in an aqueous solution buffered to pH 7.4 and maintained at 37° C.+0.5° C. and paddle mixed at an rpm of 75.

Further examples of tablet formation are provided in U.S. Pat. No. 6,669,956 which is incorporated herein by reference in its entirety.

IV. EXAMPLES

The invention is further understood by reference to the following examples, which are intended to be purely exemplary of the invention. The present invention is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only. Any methods that are functionally equivalent are within the scope of the invention. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications fall within the scope of the appended claims.

In the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

mL =	Milliliter
g =	Gram
mg =	Milligram
rpm =	revolutions per minute
min =	Minute
mm =	Millimeter
v/v =	volume/volume
° C. =	degree Celsius
LOD =	lost on drying
kp =	kilopond (= 1 kilogram (kg) or 9.807 Newtons of force)
API =	active pharmaceutical ingredient

Materials and Equipment

Compound 1
Microcrystalline Cellulose Avicel 102 (Patheon)
Emcocel 90M, JRS Pharma E9B4B11X
Starch 1500, Colorcon, (Patheon)
Plasdone S-630, ISP
Plasdone K29/32, ISP (Patheon)
Explotab JRS Pharma (Patheon)
Magnesium Stearate, Mallinkrodt
Punch & Die for 500 mg tablet, 0.3510"×0.6299", Oval Shape
Balance, AX105, Mettler-Toledo Inc.
Balance, PG3001-S, Mettler-Toledo Inc.
Tablet Friabilator (USP), Pharma Alliance
Mini Blend V-Blender, Globe Pharma
USA Standard Testing Sieves
MiniGlatt Fluid Bed Dryer, Type 3, Glatt
Tablet Hardness Tester, Holland C40 Tablet Hardness Tester, Engineering Systems
Differential Scanning calorimeter, DSC Q100 by TA Instruments
Laboratory Humidity Chamber Mod. LH-1.5, Associated Environmental Systems
X-Ray Powder Diffraction, Miniflex Tabletop XRD System by Rigaku/MSC, The Woodlands, Tex.
Stokes B-2 Rotary Tablet Press
HPLC System, Waters with Photodiode Array Detector
Dissolution Tester, Sotax Dissolution with Rainbow Monitor System
Moisture Analyzer HB43, Mettler-Toledo Inc.
Flodex Powder Flow Tester, Hanson Research Corp.
High Shear Granulator, Mod. KG-5, Key International, Inc.

Example 1

Preparation of Final Blend

A 125 g batch of Compound 1 granules were prepared by mixing Compound 1 with all the excipients except magnesium stearate (listed in Table 1) on a paper tray using a spatula, granulated with approximately 130 g of water. Granules were dried in the fluid bed at 60° C. and collected at 7.3% and 6.5% LOD. They were then milled, and blended with 2% magnesium stearate for 2 minutes to make the final blend. The formulation is shown in Table 1. The final blend was characterized and pressed into tablets. The tablets were tested for potency and impurities, hardness and dissolution. Example 2 shows a final blend composition (Table 2) using a KG-5 High Shear Granulator.

TABLE 1

Excipient	wt(g)
Compound 1	32.5
Avicel PH102	38.75
Starch 1500	40
Plasdone K29/32	3.75
Explotab	7.5
Magnesium Stearate	2.5
Total	125

Example 2

Preparation of final Blend using a KG-5 High Shear Granulator

TABLE 2

Excipient	wt(g)
Compound 1	130
MCC Avicel PH102	157.5
Starch 1500	160
Plasdone K29/32	15
Explotab	30
Magnesium Stearate	7.5
Total	500

Example 3

Preparation of Compound 1 Powder Blend

Three 500 g batches of Compound 1 powder blends (see Table 3) were prepared according to the following method. A KG-5 High Shear Granulator with an 8-inch impeller diameter was used to preblend all ingredients (except magnesium stearate) at low (155 rpm), medium (405 rpm), or high (600 rpm) impeller speeds with the chopper speed of 1200 rpm for 2 minutes. Water was added at a rate of 30 to 31.5 g/min to the powder mix. After the full amount of water was added, the mixture was blended for an additional 2 minutes. The wet granules were dried with the MiniGlatt Fluid Bed Dryer at 60°

C. to targeted LODs and the granule texture, size, shape, stickiness, etc visually inspected. Drying at various temperatures and times are evaluated also. The granules were milled through CoMill U3 with 0 32R mesh screen (0.0331 inch diameter holes), 1.5% magnesium stearate was added and mixed for 2 minutes in the V-blender to make the final blends. The final blends were checked for degradation by HPLC, and physical properties determined such as, Bulk Density, Tapped Density, Carr's Index, Hausner Ratio and Flow Index by Flodex. The final blends were compressed into 500 mg tablets using Stokes B-2 Rotary Press with 0.3071X0.6102 inches modified oval punches. The tablets were compressed with the same pressure settings to obtain maximum/achievable tablet hardness.

TABLE 3

Excipient	wt(g)
Compound 1	130
MCC Avicel PH102	157.5
Starch 1500	160
Plasdone K29/32	15
Explotab	30
Magnesium Stearate	7.5
Total	500

Carr's Index is a measure of compressibility of powder and defined as percent of (Tapped Density—Bulk Density)/Tapped Density. The higher the index, the more compressible of the powder and the poorer the flow. An index is 5 to 15% indicates excellent to good flowability. The Hausner Ratio is the ratio of Tapped Density to Bulk Density and is an assessment of interparticulate friction. A ratio of <1.6 is an indication of acceptable friction, in other words good powder flow. The maximum achievable hardness is defined as the hardness achieved with the maximum compression force.

Example 4

Physical Properties of Final Blend

Compound 1 (as the hexahydrate) was granulated with the excipients (except magnesium stearate) in Table 4. The physical properties of the final blend made by granulating Compound 1 with all the excipients together and drying to 6.5% LOD were measured and are shown in Table 5.

TABLE 4

Excipient	wt(g)
Compound 1	32.5
MCC Avicel PH102	38.75
Starch 1500	40
Plasdone K29/32	3.75
Explotab	7.5
Magnesium Stearate	2.5
Total	125

TABLE 5

Bulk Density	0.374 g/mL
Tapped Density	0.420 g/mL
Carr's Index	11.0%
Hausner Ratio	1.12
Flow Index	16 mm

The Carr's Index of 15% and a flow index of 16 mm indicate an excellent powder flow of the final blend.

Example 5

Maximum Achievable Hardness of Tablets

Tablets from final blends prepared as described in Example 4 with 7.27% and 6.47% LOD and were compressed and the hardness determined. The results are provided in Table 6. The tablet hardness was the maximum that was achievable. As demonstrated, tablets with hardness of 27.9 to 33.8 kp were obtained. All the tablets from these final blends appeared off-white and highly homogeneous. The final blend with 6.47% was compressed to tablets with hardness of 20 kp and 30 kp. The tablets displayed >75% dissolution after 30 minutes, indicating a large tolerance with respect to the hardness of tablets.

TABLE 6

Weight, mg	Hardness, kp	Thickness, mm
LOD of Final Blend = 7.27%		
500	27.9	4.98
504	29.8	5.05
501	29.1	5.04
LOD of Final Blend = 6.47%		
505	33.8	5.06
506	32.2	5.08
505	33.8	5.08

Example 6

Stability of Compound 1 in Tablets

Tablets from Example 5 were stored under intensified shelf-life conditions (one month at 40° C. and 75% Relative Humidity) and analyzed for purity and potency by HPLC. Analysis results for tablets after one month at the aforementioned showed a purity of 98.8-99.1%.

Example 7

Dependence of Tablet Hardness on Density of Blend

Select batches of granules which were produced by methods described in Example 3, were further subjected to the various granulation parameters shown in Table 7. The impeller speed was varied and it was observed that low impeller speeds lead to less dense granules. In addition, the amount of water sprayed during the process was evaluated and it was found that less water sprayed may also help to lower the density of granules.

TABLE 7

Batch	A	B	C
Batch Size, g	500	500	450
Impeller Speed, rpm	405	600	155
Chopper Speed, rpm	2000	2000	1200
Water added g/min	30	30	31.5
Water consumed, g	250	260	185
LOD of wet granules	37.1%	38.9%	33.7%
LOD of dry granules	6.5%	6.0%	6.6%
Bulk Density, g/mL	0.570	0.621	0.505

TABLE 7-continued

Batch	A	B	C
Tapped Density, g/mL	0.632	0.674	0.583
Hausner Ratio	1.11	1.09	1.15
Carr's Index	9.81	7.86	13.4
Flow Index	14 mm	14 mm	14 mm

* Batch C is a combination of three independent batches. Experimental procedures for Batch A, B, C are the same except the Impeller speed, chopper speed, rate and amount of water added.

All the granules possess excellent flow properties as measured by Hauser ratio, Carr's index and flow index. The LOD of dry granules, 6.0 to 6.6%, is close to 7.1% as in the starting blend. These blends appeared ideal for tablet compression.

Tablets were compressed from these blends after blending with magnesium stearate at the maximum compression force. Results are summarized in Table 8. The less dense the blend, the harder the tablets. The blend with density of 0.65 g/mL resulted in tablets with the maximum hardness of 5-8 kp.

TABLE 8

Tablet wt, mg	Hardness, kp	Thickness, mm
Maximum Tablet Hardness for Batch A: Bulk Density 0.570 g/Ml		
517	20.8	5.09
521	20.2	5.18
516	19.2	5.21
Maximum Tablet Hardness for Batch B: Bulk Density 0.621 g/mL		
501	17.3	4.91
502	16.3	4.93
502	15.0	4.94
Maximum Tablet Hardness for Batch C: Bulk Density 0.505 g/mL		
507	35.9	5.01
502	35.4	4.99
500	33.7	4.98

Example 8

Moisture Content (LOD) Vs. Hardness of Tablets with Density of the Blend <0.55 g/mL

The granules from Batch A (Example 7) were dried at 50° C., 60° C. and 70° C. to LOD of 6.4 to 6.8%. The dried granules were assayed by HPLC. The purity/impurity profiles remained the same for the three drying conditions. Compared to API, there was 0.15% decrease in purity and the same amount of increase in Compound 2. The tablets compressed from Batch A were dried and analyzed via HPLC and gave similar results to the granules. The dissolution of the tablets was >75% after 30 min.

Example 9

Moisture content (LOD) vs. Hardness

Batch C (Example 7) was further dried in 6×65 g lots (Labeled C-1 to C-6) to LOD of 4.7, 5.6, 6.7, 7.6, 8.7 and 9.3%. All the dried granules were milled through CoMil with #25 mesh screen, and mixed with 1.5% magnesium stearate for 2 minutes. The physical properties of the final blends are summarized in Table 9.

TABLE 9

	C-1	C-2	C-3	C-4	C-5	C-6
LOD, %	4.70	5.58	7.55	6.74	8.74	9.33
Sample Weight, g	51.2	50.1	48.9	51.1	48.3	49.8
Bulk Density, g/mL	0.517	0.506	0.499	0.511	0.503	0.507
Tapped Density, g/mL	0.595	0.589	0.579	0.581	0.574	0.586
Carr's Index	13.1	14.1	13.8	12.1	12.4	13.5
Hausner Ratio	1.15	1.16	1.16	1.14	1.14	1.16

The final blends C-1-C-6 from Table 9 were compressed separately into 500 mg tablets under the same maximum compression force. LOD of the final blends, weight, hardness and thickness of the tablets are provided in Table 10.

TABLE 10

	wt, mg	Hardness, kp	Thickness, mm
Tablet C-1	477	29.2	4.85
LOD = 4.70%	513	32.5	5.08
	514	34.4	5.09
Tablet C-2	516	35.2	5.04
LOD = 5.58%	511	31.3	5.08
	500	31.9	4.99
Tablet C-4	507	35.9	5.01
LOD = 6.74%	502	35.4	4.99
	500	33.7	4.98
Tablet C-3	502	33.0	4.94
LOD = 7.55%	500	33.0	4.92
	503	32.7	4.95
Tablet C-5	502	29.5	4.93
LOD = 8.74%	500	29.0	4.94
	503	26.0	4.94
Tablet C-6	506	26.9	4.97
LOD = 9.33%	505	26.4	4.97
	505	27.0	4.99

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entireties.

Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

What is claimed is:

1. A wet granulated formulation comprising water, a therapeutically effective amount of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt and a sufficient amount of a water sequestering agent to inhibit decomposition of (6-(5-fluoro-2-(3,4,5-trimethoxyphenyl-amino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl) methyl phosphate disodium salt, wherein said wet granulated formulation after drying has a bulk density sufficient to form tablets having a hardness in the range of about 6 kp to about 30 kp.

2. The formulation of claim **1**, wherein after drying the formulation has a bulk density of between about 0.35 to about 0.65 g/mL.

3. The formulation of claim 1, wherein the water sequestering agent is selected from the group consisting of starch, magnesium sulfate, calcium chloride, silica gel, and kaolin.

4. The formulation of claim 3, wherein the water sequestering agent is starch.

5. The formulation of claim 4, wherein the starch is partially pregelatinized.

6. The formulation of claim 5, wherein the starch is derived from Maize.

7. The formulation of claim 1 which further comprises at least one of a filler, a lubricant, a suspending/dispersing agent, a binding agent, and a disintegrant.

8. A wet granulating process, comprising:

a) blending a composition comprising (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt and a sufficient amount of a water sequestering agent to inhibit the decomposition of 6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt to form a blended mixture;

b) granulating the blended mixture of a) while adding water to form wet granules;

c) drying the wet granules of b) at below 65° C. until a loss on drying of between about 5% and 11% is achieved to provide dried granules; and

d) blending a lubricant into the dried granules of c) to provide blended granules.

9. The method of claim 8, further comprising:

compressing the blended granules to form tablets.

* * * * *

EXHIBIT D

US008771648B2

(12) **United States Patent**
Gururajan et al.

(10) **Patent No.: US 8,771,648 B2**
(45) **Date of Patent: Jul. 8, 2014**

(54) **(TRIMETHOXYPHENYLAMINO) PYRIMIDINYL FORMULATIONS**

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USPC **424/43**; 424/400; 424/466; 544/51; 514/81

(58) **Field of Classification Search**
None
See application file for complete search history.

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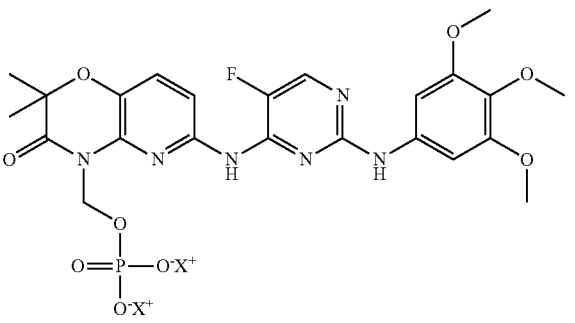
(57) **ABSTRACT**

There are provided pharmaceutical compositions comprising greater than 15% w/w of a compound of Formula (I) as defined herein and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients; and to processes for obtaining them.

Formula (I)



8 Claims, 9 Drawing Sheets

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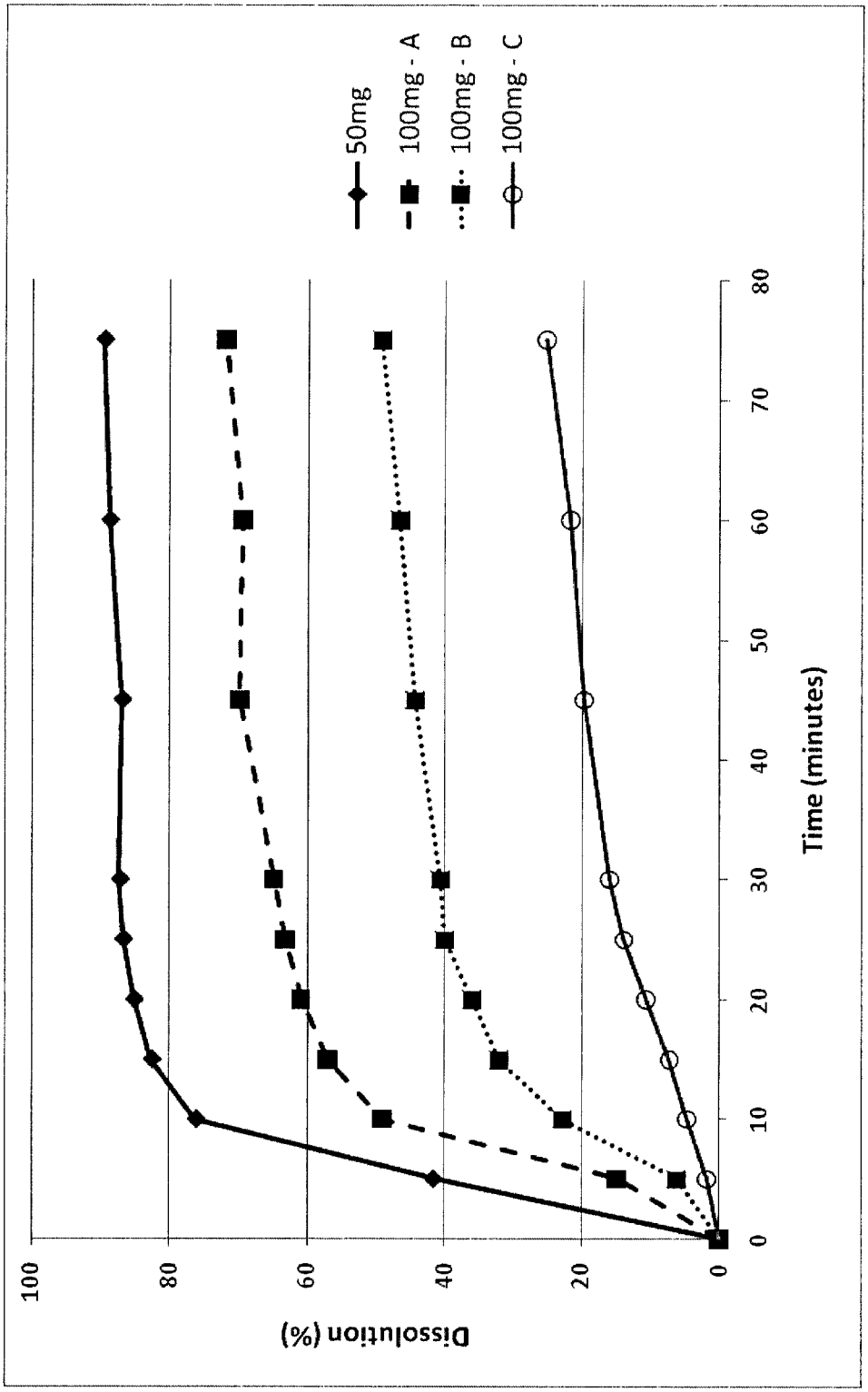

50mg
100mg - A
100mg - B
100mg - C
Dissolution (%)
0
20
40
60
80
100
Time (minutes)
0
10
20
30
40
50
60
70
80

Figure 1

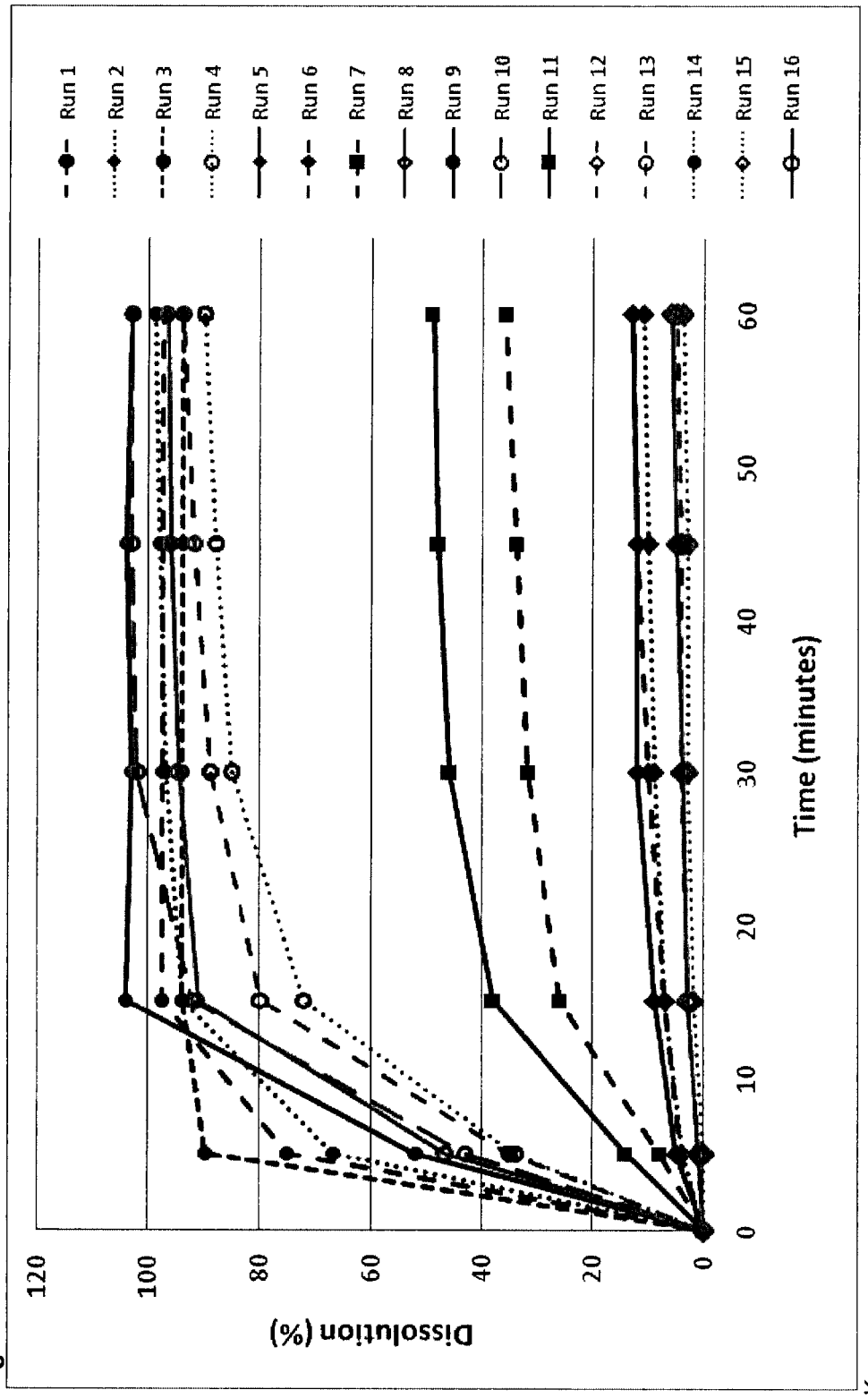


Figure 2

Key:
●○ Satisfactory dissolution – runs 1, 3, 4, 9, 10, 13, 14, 16
■ Low dissolution – runs 7, 11
◆◇Very low dissolution – runs 2, 5, 6, 8, 12, 15

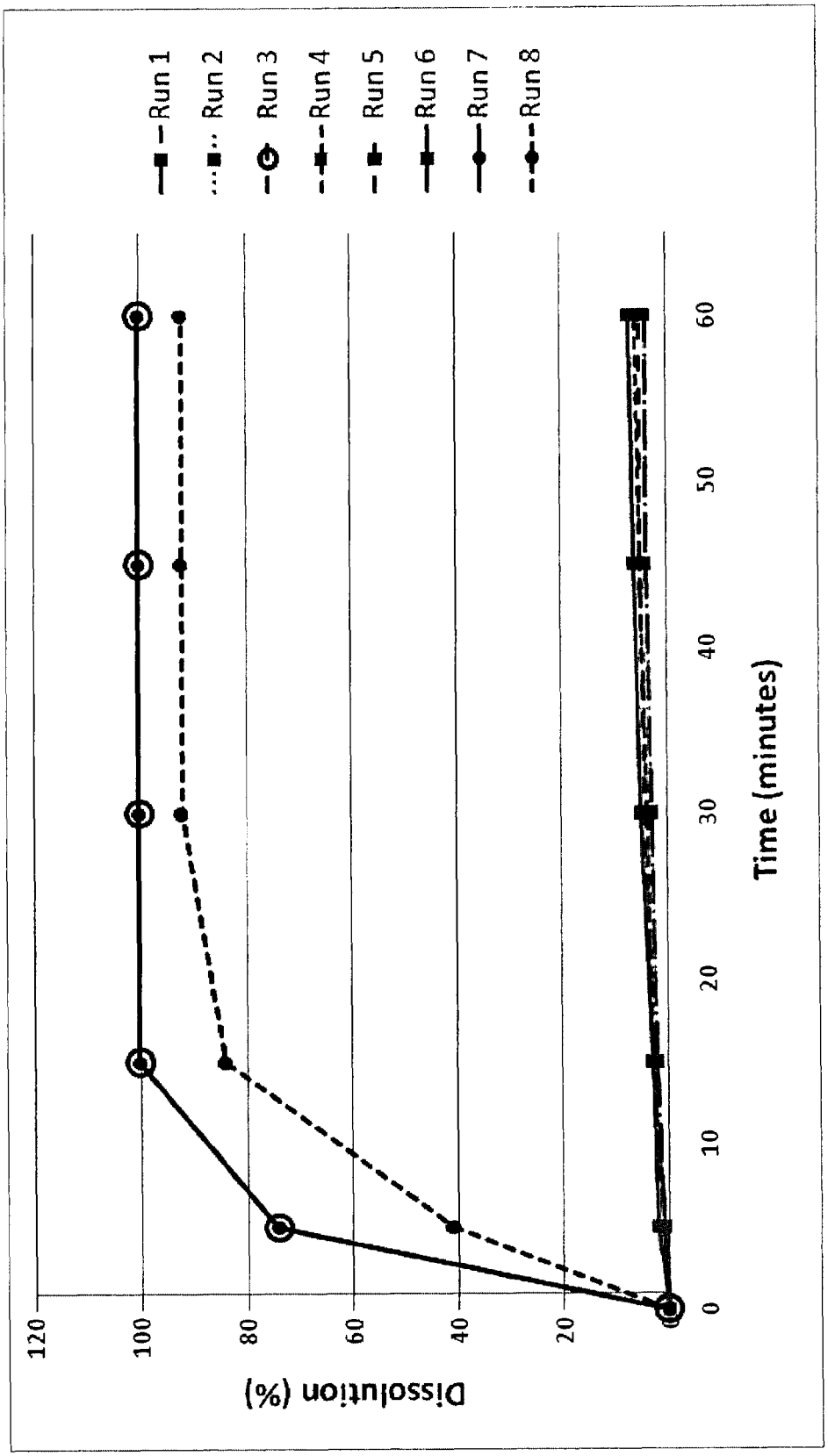

Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Dissolution (%)
120
100
80
60
40
20
0
10
20
30
40
50
60
Time (minutes)
Key:
●○ Satisfactory dissolution – runs 3,7,8
■ Low dissolution – runs 1,2,4,5,6

Figure 3

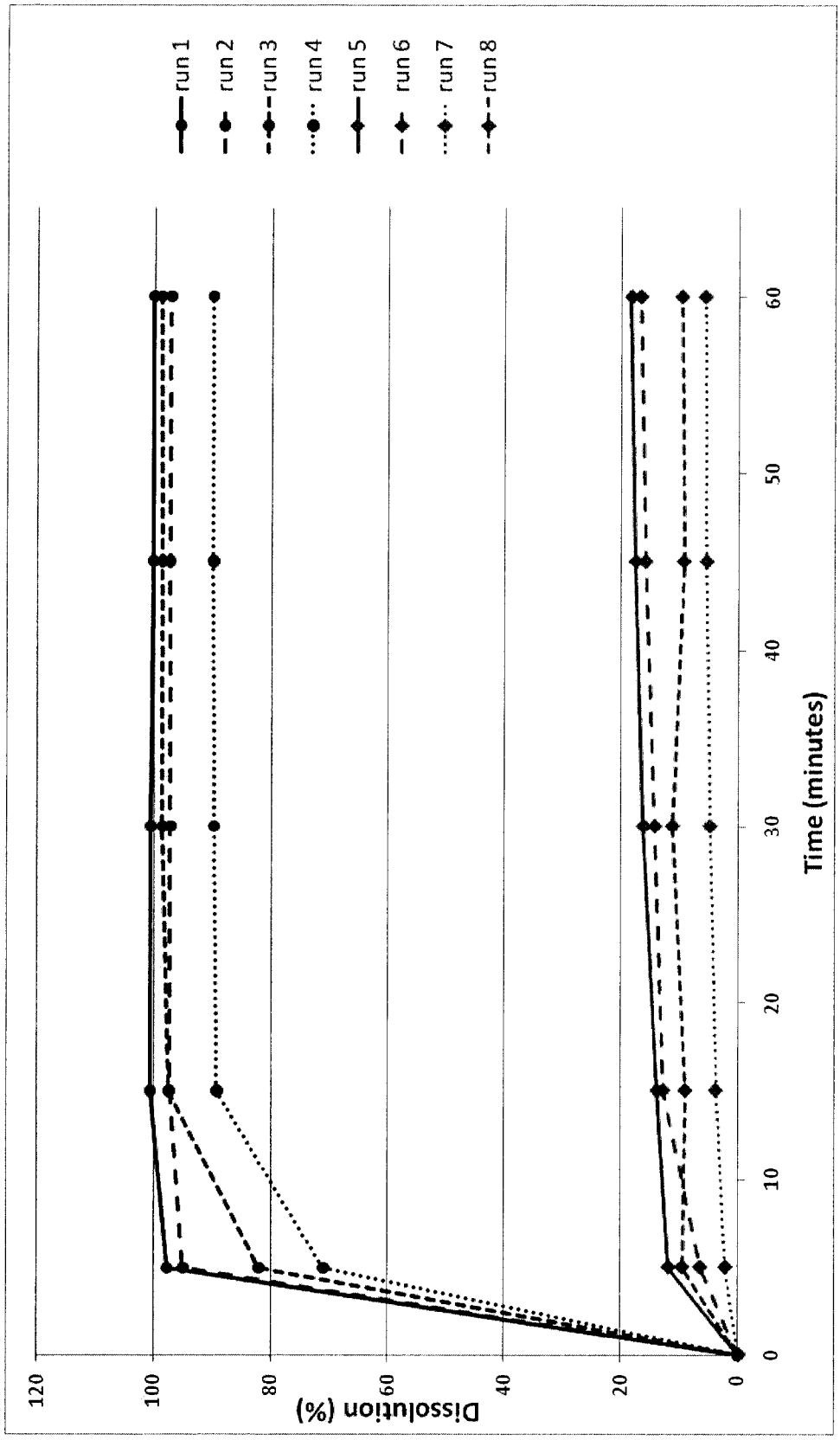

run 1
run 2
run 3
run 4
run 5
run 6
run 7
run 8
Dissolution (%)
0
20
40
60
80
100
120
Time (minutes)
0
10
20
30
40
50
60
Key:
● Satisfactory dissolution – runs 1, 2, 3, 4
◆ Low dissolution – runs 5, 6, 7, 8

Figure 4

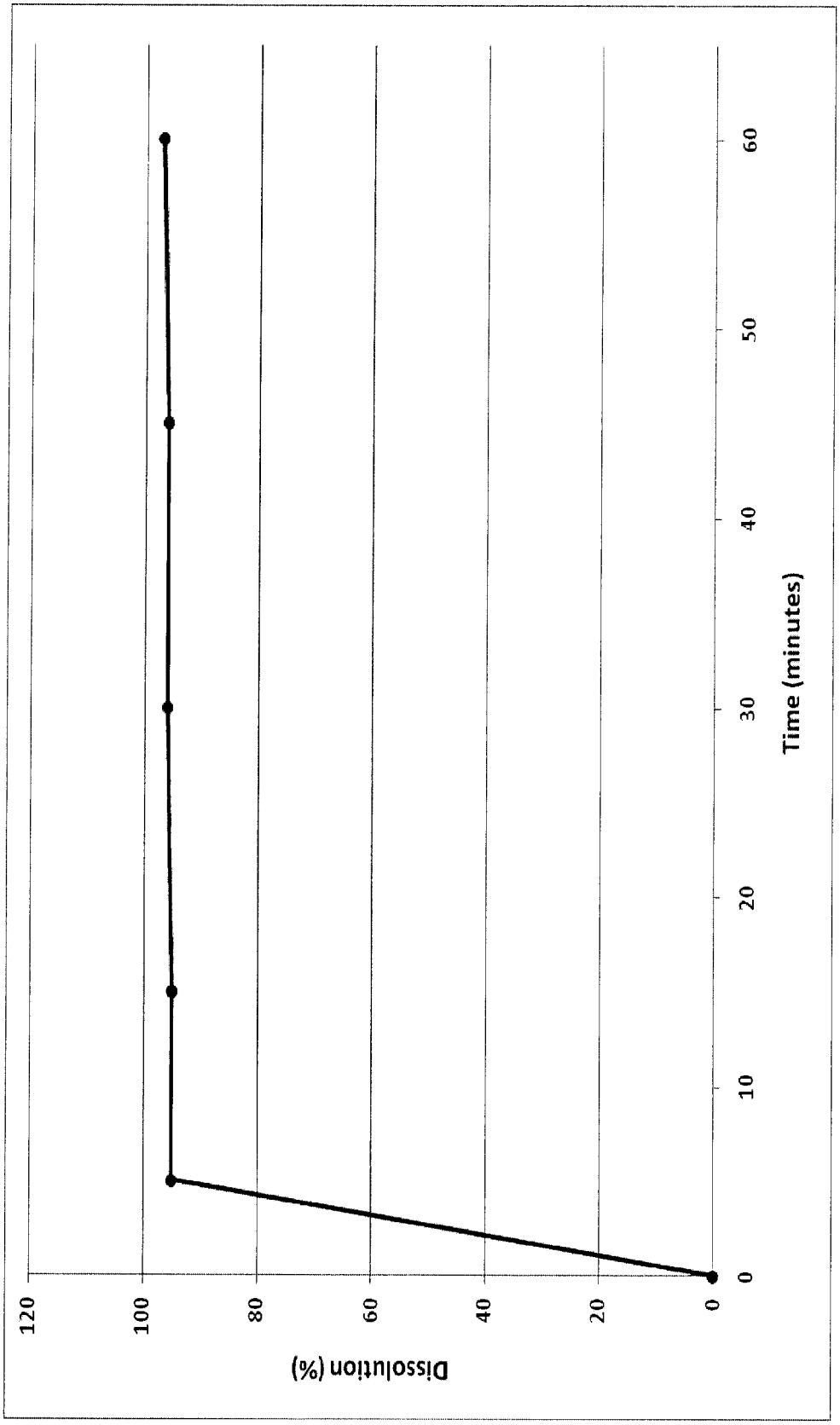

Dissolution (%)
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minutes)

Figure 5

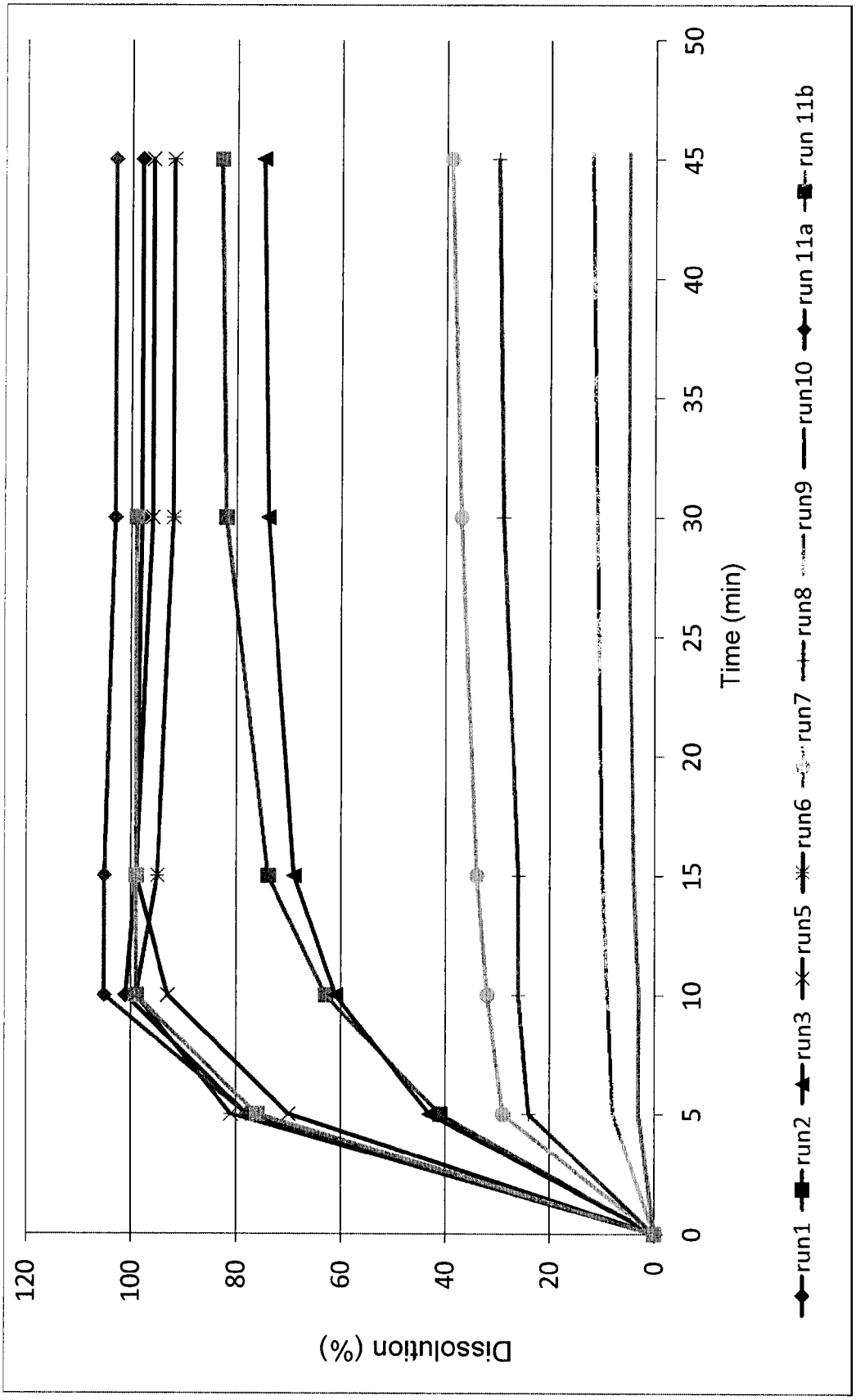

Dissolution (%)
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
50
Time (min)
run1
run2
run3
run5
run6
run7
run8
run9
run10
run 11a
run 11b

Figure 6

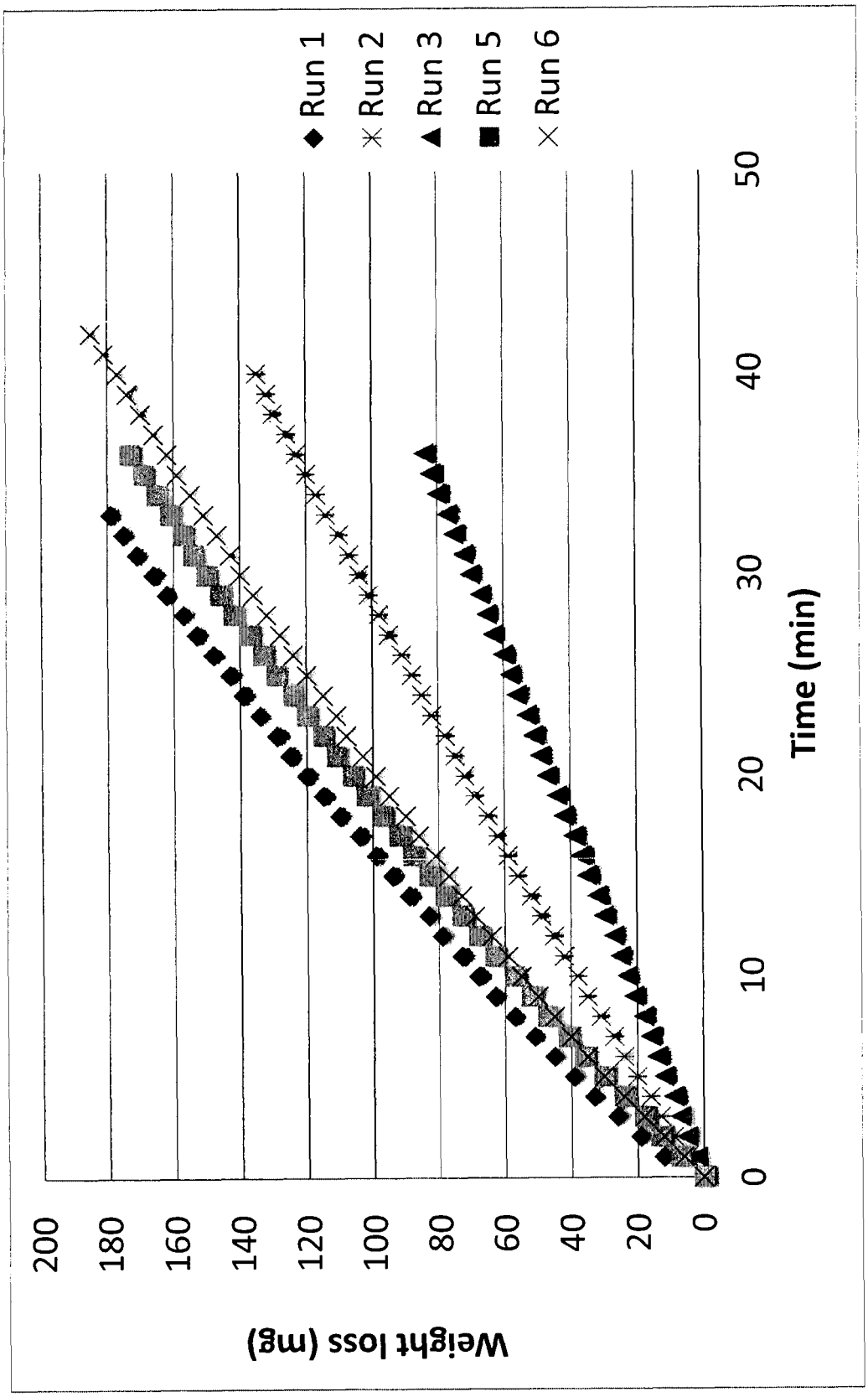

Run 1
Run 2
Run 3
Run 5
Run 6
Weight loss (mg)
0
20
40
60
80
100
120
140
160
180
200
Time (min)
0
10
20
30
40
50

Figure 7

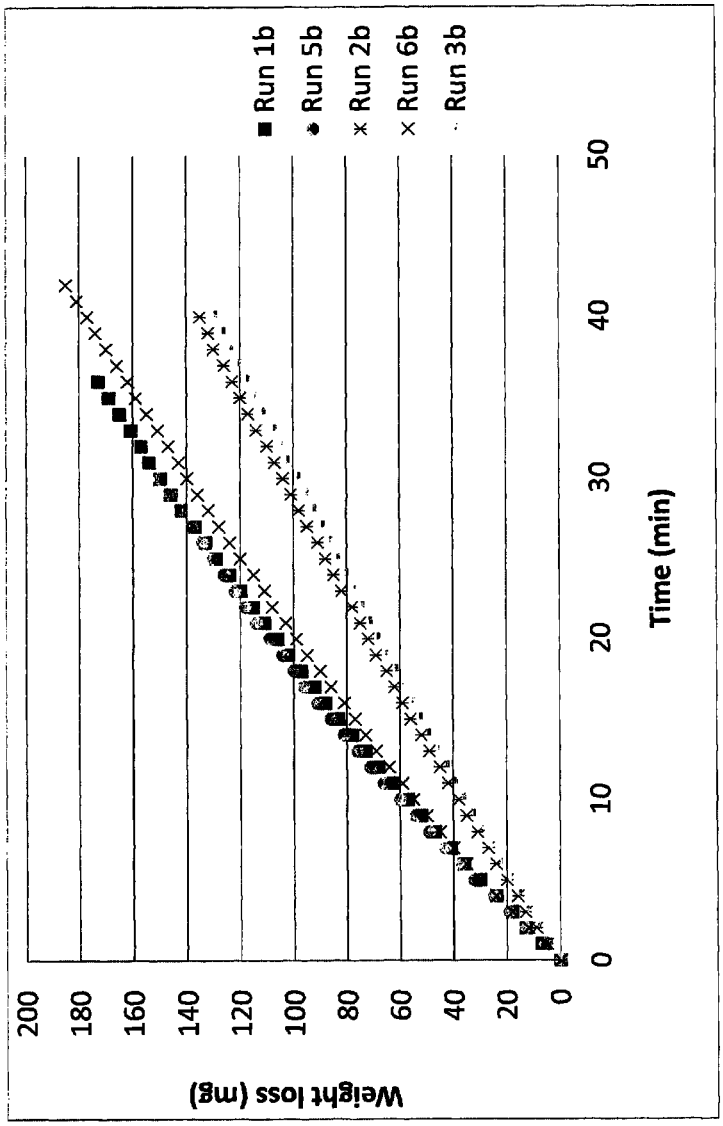

Run 1b
Run 5b
Run 2b
Run 6b
Run 3b
Weight loss (mg)
200
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
Time (min)

Figure 8

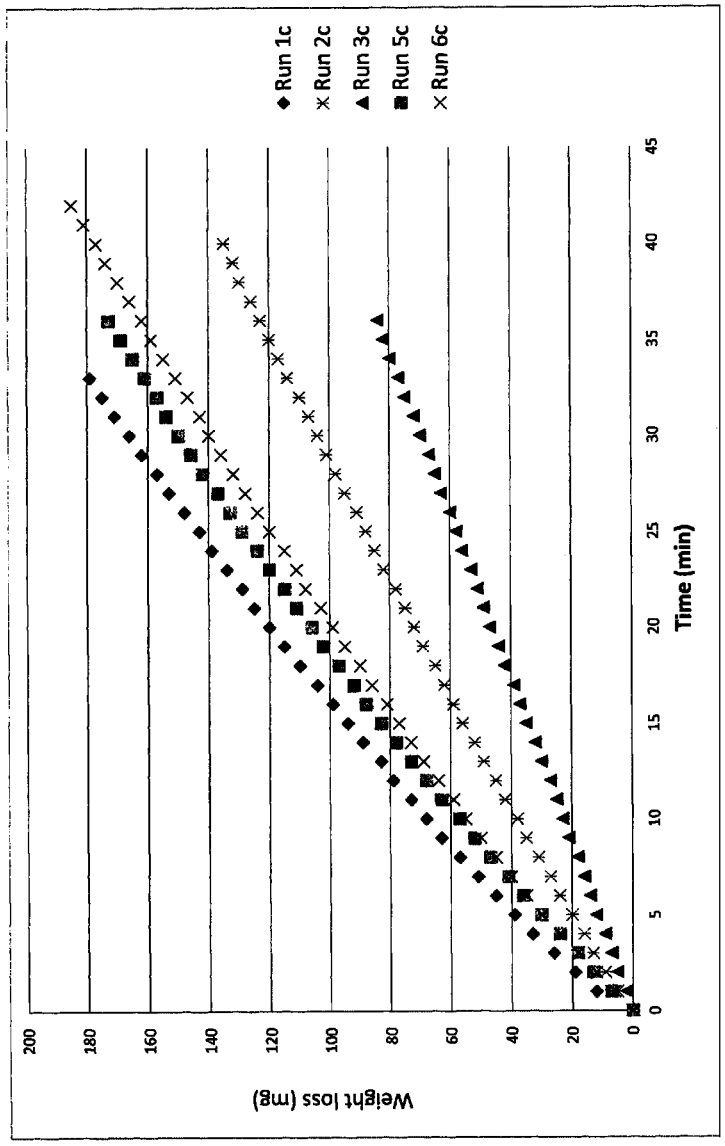

Run 1c
Run 2c
Run 3c
Run 5c
Run 6c
Weight loss (mg)
Time (min)
0
20
40
60
80
100
120
140
160
180
200
0
5
10
15
20
25
30
35
40
45

Figure 9

(TRIMETHOXYPHENYLAMINO) PYRIMIDINYL FORMULATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. Application No. 61/512,621 filed on 28 Jul. 2011.

FIELD OF THE INVENTION

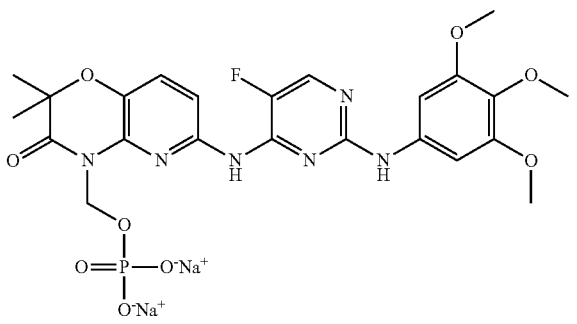
The present invention relates to pharmaceutical/formulation chemistry. The invention is understood to apply generally to formulations of compounds which contain an increased percent loading of the active ingredient. As a preferred aspect, provided herein are formulations of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt (Compound I) which contain an increased percent loading of Compound I. The formulations are useful for treating a variety of diseases including, but not limited to, lymphoma, immune (idiopathic) thrombocytopenia purpura (ITP), and rheumatoid arthritis (RA).

BACKGROUND OF THE INVENTION

In the manufacture of pharmaceutical formulations, it may be desirable for the drug to be administered using the smallest possible number of tablets. Thus it may be desirable for a patient to take the required dose of a drug in a single tablet rather than in more than one tablet, or in two tablets rather than in more than two tablets. Accordingly, it may be desirable for a pharmaceutical formulation to contain an increased percent loading of the active ingredient. However, it is known that increasing the percent loading of active ingredient may lead to a pharmaceutical formulation which exhibits unsatisfactory and/or variable dissolution or to a formulation which exhibits unsatisfactory and/or variable bioavailability. Such formulations may be unsuitable for use by patients.

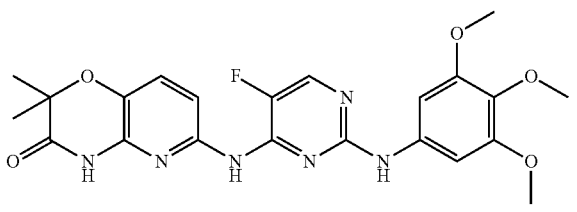
Compound I (below) is disclosed in international patent application WO2006/078846.

Compound (I)



Compound I is a pro-drug of Compound II (below). Compound II is disclosed in international patent application WO2005/016893.

Compound (II)



Hydrolytically stable pharmaceutical formulations of Compound I which include a water sequestering agent and which are prepared by a wet granulation process are disclosed in international patent application WO2009/061909.

Javaid et al (J. Pharm. Sci. 61 (9) 1972 pp 1370-1373) studied the effect of various classes of buffering agents on the dissolution of aspirin from tablet formulations.

Compound I is currently in clinical studies for the treatment of a variety of diseases such as lymphoma, ITP and RA. Dosing is currently done with orally delivered tablets with a tablet strength of 50 mg. These tablets exhibit satisfactory dissolution at low pH. However, these tablets contain a relatively low percent loading (12.5% w/w) of Compound I.

Tablets with a tablet strength of 100 mg contain an increased percent loading of Compound I. However, these tablets may exhibit unsatisfactory and/or variable dissolution at low pH. Furthermore, these tablets may exhibit unsatisfactory and/or variable bioavailability of the active ingredient.

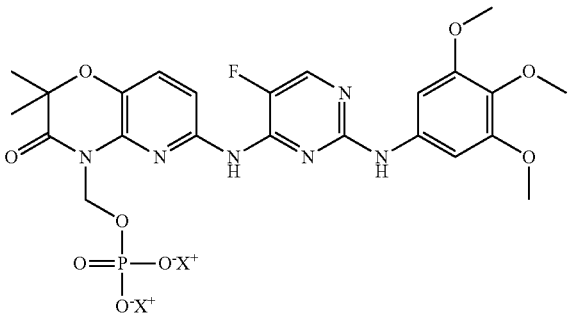
It is desirable, therefore, to produce new pharmaceutical formulations of Compound I which overcome at least in part the above problems.

DESCRIPTION OF THE INVENTION

This invention is generally directed to formulations of compounds which contain an increased percent loading of the compound of formula (I), in particular to formulations which contain an increased percent loading of active ingredient and exhibit satisfactory dissolution at low pH.

The compound of formula (I) (known hereafter as "Formula (I)") is shown below:

Formula (I)



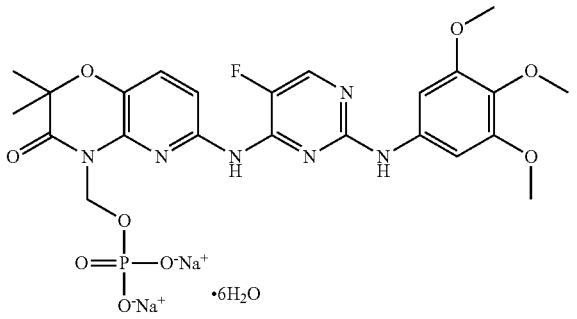
wherein each X^+ represents a monovalent cation, for example a monovalent metal cation, such as a sodium cation (Na^+), a potassium cation (K^+) or a lithium cation (Li^+); or wherein X^+ and X^+ are taken together to represent a divalent cation X^{2+}, for example a divalent metal cation, such as a magnesium cation (Mg^{2+}), a calcium cation (Ca^{2+}) or a barium cation (Ba^{2+});

and/or hydrates thereof (such as the hexahydrate).

For example, Formula (I) may be in the form of Compound (I) above.

In another particular example, Formula (I) may be in the hexahydrate form of Compound (I) (which form is known hereafter as "Formula (II)"). The compound of Formula (II) is shown below.

Formula (II)



In particular, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and one or more effervescent agents allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and sodium hydrogen carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a yet further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and potassium hydrogen carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and magnesium carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and sodium carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and calcium carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and potassium carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention, there is provided a pharmaceutical composition in unit dosage form comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof (for example 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg or 200 mg) and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients. For the avoidance of doubt, each of the previous integers represents a separate and independent aspect of the invention.

In another aspect of the invention a unit dosage form of the pharmaceutical composition comprises between about 60 mg to about 300 mg of Formula (I) and/or hydrate thereof.

In another aspect of the invention a unit dosage form of the pharmaceutical composition comprises between about 60 mg to about 250 mg of Formula (I) and/or hydrate thereof.

In a still further aspect, a unit dosage form of the pharmaceutical composition comprises between about 100 mg to about 200 mg of Formula (I) and/or hydrate thereof.

In a yet further aspect, a unit dosage form of the pharmaceutical composition comprises between about 125 mg to about 190 mg of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, a unit dosage form of the pharmaceutical composition comprises 63 mg±3 mg of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, a unit dosage form of the pharmaceutical composition comprises 126 mg±13 mg of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, a unit dosage form of the pharmaceutical composition comprises 190 mg±19 mg of Formula (I) and/or hydrate thereof.

In another aspect of the invention the pharmaceutical composition comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the pharmaceutical composition comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the pharmaceutical composition comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the pharmaceutical composition comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the pharmaceutical composition comprises 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the pharmaceutical composition comprises 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the pharmaceutical composition comprises less than or equal to 30% w/w of one or more effervescent agents.

In a still further aspect of the invention, the pharmaceutical composition comprises less than or equal to 25% w/w of one or more effervescent agents.

In a further aspect, the pharmaceutical composition comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the pharmaceutical composition comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the pharmaceutical composition comprises less than or equal to 10% w/w of one or more effervescent agents.

In a yet further aspect, the pharmaceutical composition comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 125 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 125 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 190 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 190 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 225 mg of Formula (I) and/or hydrate thereof and less than or equal to 150 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 225 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further embodiment of the invention, the pharmaceutical composition and/or unit dosage form does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or hydrate thereof.

In a further aspect of the invention, optional ingredients which can be added to the pharmaceutical composition include one or more of the following:

a) fillers which, when employed, range between for example about 35 to about 75 weight percent (e.g. about 50 to about 70 weight percent) of the dry formulation;
b) binding agents which, when employed range between for example about 2 to about 8 weight percent of the dry formulation;
c) lubricants which, when employed, range from between about 0.25 and 2.0 weight percent of the dry formulation;
d) disintegrants which, when employed, range from between about 0.5 and 10.0 weight percent (e.g. about 5 weight percent) of the dry formulation; and
e) water sequestering agents, which, when employed, range from between about 2 weigh percent and 40 weight percent of the dry formulation.

In a further aspect of the invention, the pharmaceutical composition further comprises one or more additional ingredients independently selected from, for example

a) fillers such as mannitol (e.g. Pearlitol 50c, Peralitol 120c or Pearlitol 160c) or microcrystalline celluloses (e.g. MCC Avicel PH 102, Emcocel 90M, etc.);
b) binding agents such as Plasdone K29/32, Povidone, microcrystalline celluloses or Kollidon K30;
c) lubricants such as magnesium stearate;
d) disintegrants such as sodium starch glycolate, for example ExploTab or Glycolys LV;
e) Water sequestering agents such as starch (e.g. sodium starch glycolate), magnesium sulfate, calcium chloride, silica, kaolin, microcrystalline celluloses etc.

In another aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention, there is provided a tablet comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof (for example 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg or 200 mg) and an amount of one or more effervescent agents (that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients. For the avoidance of doubt, each of the previous integers represents a separate and independent aspect of the invention.

In another aspect of the invention, the tablet comprises between about 60 mg to about 300 mg of Formula (I) and/or hydrate thereof.

In another aspect of the invention the tablet comprises between about 60 mg to about 250 mg of Formula (I) and/or hydrate thereof.

In a still further aspect, the tablet comprises between about 100 mg to about 200 mg of Formula (I) and/or hydrate thereof.

In a yet further aspect, the tablet comprises between about 125 mg to about 190 mg of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the tablet comprises 63 mg±3 mg of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the tablet comprises 126 mg±13 mg of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the tablet comprises 190 mg±19 mg of Formula (I) and/or hydrate thereof.

In another aspect of the invention the tablet comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the tablet comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the tablet comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the tablet comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the tablet comprises 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the tablet comprises 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the tablet comprises less than or equal to 30% w/w of one or more effervescent agents.

In a further aspect, the tablet comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the tablet comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the tablet comprises less than or equal to 10% w/w of one or more effervescent agents.

In a further aspect of the invention, the tablet comprises less than or equal to 75 mg of one or more effervescent agents.

In a yet further aspect, the tablet comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further aspect of the invention, there is provided a tablet comprising greater than or equal to 125 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further aspect of the invention, there is provided a tablet comprising greater than or equal to 125 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a tablet comprising greater than or equal to 190 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a tablet comprising greater than or equal to 190 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a tablet comprising greater than or equal to 225 mg of Formula (I) and/or hydrate thereof and less than or equal to 150 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a tablet comprising greater than or equal to 225 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further embodiment of the invention, the tablet does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or a hydrate thereof.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral administration.

These dosage forms will usually include one or more pharmaceutically acceptable excipients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings or colorants. It will be understood that an individual excipient may be multifunctional. Examples of pharmaceutically acceptable excipients are described in the Handbook of Pharmaceutical Excipients (Fifth Edition, 2005, edited by Ray C. Rowe, Paul J. Sheskey and Sian C. Owen, published by the American Pharmaceutical Association and the Pharmaceutical Press). The active ingredients of the present invention may be administered by oral or parenteral (e.g. intravenous, subcutaneous, intramuscular or intraarticular) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. The active ingredients may also be delivered to the lung and/or airways via oral administration in the form of a solution, suspension, aerosol or dry powder formulation. As will be understood by those skilled in the art, the most appropriate method of administering the active ingredients is dependent on a number of factors.

It will be understood that the therapeutic dose of each active ingredient administered in accordance with the present invention will vary depending upon the particular active

ingredient employed, the mode by which the active ingredient is to be administered, and the condition or disorder to be treated.

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

In a further aspect of the invention, optional ingredients which can be added to the compositions disclosed herein include one or more of the following:

a) fillers which, when employed, range between for example about 35 to about 75 weight percent (e.g. about 50 to about 70 weight percent) of the dry formulation;

b) binding agents which, when employed range between for example about 2 to about 8 weight percent of the dry formulation;

c) lubricants which, when employed, range from between about 0.25 and 2.0 weight percent of the dry formulation;

d) disintegrants which, when employed, range from between about 0.5 and 10.0 weight percent (e.g. about 5 weight percent) of the dry formulation; and

a) water sequestering agents, which, when employed, range from between about 2 weigh percent and 40 weight percent of the dry formulation;

In a further aspect of the invention, the tablet further comprises one or more additional ingredients independently selected from, for example:

a) fillers such as mannitol (e.g. Pearlitol 50c, Peralitol 120c or Pearlitol 160c) or microcrystalline celluloses (e.g. MCC Avicel PH 102, Emcocel 90M, etc.);

b) binding agents such as Plasdone K29/32, Povidone, microcrystalline celluloses or Kollidon K30;

c) lubricants such as magnesium stearate;

d) disintegrants such as sodium starch glycolate, for example ExploTab or Glycolys LV;

a) Water sequestering agents such as starch (e.g. sodium starch glycolate), calcium chloride, silica, kaolin, microcrystalline celluloses etc.

In a further aspect of the invention, the pharmaceutical composition or unit dosage form comprises the compound of Formula (I) and/or hydrate thereof, one or more effervescent agents and a filler (such as mannitol). In a further aspect of the invention, the pharmaceutical composition or unit dosage form comprises the compound of Formula (I) and/or hydrate thereof, one or more effervescent agents, a filler (such as mannitol) and a binding agent (such as Povidone). In a further aspect of the invention, the pharmaceutical composition or unit dosage form comprises the compound of Formula (I) and/or hydrate thereof, one or more effervescent agents, a filler (such as mannitol), a binding agent (such as Povidone) and a disintegrant (such as sodium starch glycolate). In another aspect the pharmaceutical composition or unit dosage form comprises the compound of Formula (II), one or more effervescent agents, a filler (such as mannitol), a binding agent (such as Povidone), a disintegrant (such as sodium starch glycolate) and a lubricant (such as magnesium stearate).

In a yet further aspect of the invention, the pharmaceutical composition comprises the following components by weight:

Composition 1 (mg)	
Formula (II)	126
Mannitol	249
Sodium hydrogen carbonate	75
Sodium starch glycolate	25
Povidone	15
Magnesium stearate	10

Composition 2 (mg)	
Formula (II)	190
Mannitol	185
Sodium hydrogen carbonate	75
Sodium starch glycolate	25
Povidone	15
Magnesium stearate	10

Composition 3 (mg)	
Formula (II)	63
Mannitol	62
Sodium hydrogen carbonate	25
Sodium starch 8 glycolate	
Povidone	5
Magnesium stearate	3

In a yet further aspect of the invention, the pharmaceutical composition comprises the following components (% w/w):

Composition 1 (% w/w)	
Formula (II)	25
Mannitol	50
Sodium hydrogen carbonate	15
Sodium starch glycolate	5
Povidone	3
Magnesium stearate	2

Composition 2 and 3 (% w/w)	
Formula (II)	38
Mannitol	37
Sodium hydrogen carbonate	15
Sodium starch glycolate	5
Povidone	3
Magnesium stearate	2

In a still further aspect, the invention comprises a tablet formed from the pressing of Composition 1 and/or Composition 2 into tablet form. In a still further aspect, the invention comprises a tablet formed from the pressing of Composition 3 into tablet form.

In a separate aspect of the invention, there is provided a process for the preparation of a pharmaceutical composition, as hereinbefore defined, which process comprises bringing into association Formula (I) and/or hydrate thereof with a pharmaceutically acceptable adjuvant, diluents or carrier.

In a further aspect of the invention, there is provided a process for the preparation of a pharmaceutical composition which process comprises mixing Formula (I) and/or hydrate thereof with one or more effervescent agents optionally in the presence of one or more pharmaceutically acceptable ingredients (Step A). In a further aspect, Step A is carried out in the presence of one or more fillers (such as mannitol) and optionally in the presence of one or more pharmaceutically acceptable ingredients. In a still further aspect, Step A is carried out in the presence of one or more fillers (such as mannitol) and optionally in the presence of one or more binding agents and/or one or more disintegrants.

In a further aspect of the invention, there is provided a further process for the preparation of a pharmaceutical composition as defined above which process comprises adding purified water and/or binder solution into the powder mixture from Step A above and mixing to form enlarged granules and optionally passing through a filter screen to break-up large agglomerates (Step B). In a further aspect between about 10% and 45% by weight of purified water is added into the powder mixture.

In a further aspect of the invention, there is provided a further process for the preparation of a pharmaceutical composition which process comprises drying the enlarged granules produced in Step B above until an LOD of less than 10% (e.g. less than 5%) is achieved, to provide dried granules (Step C).

In a further aspect of the invention there is provided a process for the preparation of a pharmaceutical composition which process (wet granulation process) comprises:

a) blending Formula (I) and/or hydrate thereof with one or more effervescent agents, one or more fillers (such as mannitol) and optionally in the presence of one or more binding agents and/or one or more disintegrants and/or one or more other excipients;

b) adding between about 10% and 45% by weight of purified water and/or binder solution into the powder mixture of a) above and mixing to form enlarged granules and optionally passing through a filter screen to break-up large agglomerates; and

c) drying the enlarged granules produced in b) above until an LOD of less than 10% (e.g. less than 5%) is achieved, to provide dried granules.

The dried granules prepared in the methods above are typically between about 25 μm to about 2000 μm in diameter.

In another of its method aspects, this invention further comprises milling the dried granules. In one aspect, the dried granules are milled so that about 90 weight percent have a particle size between about 25 μm to about 2000 μm in diameter.

In yet another aspect, the dried, milled, granules are mixed with a lubricant until homogenous, and then the resulting pharmaceutical composition is tabletted. Suitable lubricants include stearic acid (e.g. magnesium stearate), colloidal silica and talc.

In an alternative aspect of the invention, the lubricant (such as magnesium stearate) can be added to the dry granules prior to milling, and then the resulting pharmaceutical composition is milled and then tabletted.

In another aspect, this invention provides a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of an effervescent that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the wet granulation formulation comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the wet granulation formulation comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the wet granulation formulation comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the wet granulation formulation comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the wet granulation formulation contains 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the wet granulation formulation contains 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the wet granulation formulation comprises less than or equal to 30% w/w of one or more effervescent agents.

In a further aspect, the wet granulation formulation comprises less than or equal to 25% w/w of one or more effervescent agents.

In a further aspect, the wet granulation formulation comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the wet granulation formulation comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the wet granulation formulation comprises less than or equal to 10% w/w of one or more effervescent agents.

In a yet further aspect, the wet granulation formulation comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the wet granulation formulation comprises Formula (I) and/or hydrate thereof, water, one or more effervescent agents, filler(s), binding agent(s) and disintegrant(s).

In a still further embodiment of the invention, the wet granulation formulation does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or a hydrate thereof.

In another aspect, this invention provides a tablet formed by compressing the wet granulation formulation.

In a further aspect of the invention, there is provided a further process for the preparation of a pharmaceutical composition as defined above which process comprises passing the mixture of Step A above through a compactor to produce dry granules (Step D).

In a further aspect of the present invention there is provided a process for the manufacture of a pharmaceutical composition which process (roller compaction process) comprises:

(a) blending Formula (I) and/or hydrate thereof with one or more effervescent agents, one or more fillers (such as mannitol) and optionally in the presence of one or more binding agents and/or one or more disintegrants and/or one or more other excipients;

(b) passing the mixture of (a) above through a compactor to produce dry granules.

The dried granules prepared in the methods above are typically between about 25 μm to about 2000 μm in diameter.

In another of its method aspects, this invention further comprises milling the dried granules. In one aspect, the dried granules are milled so that about 90 weight percent have a particle size between about 25 μm to about 2000 μm in diameter.

In another aspect, a lubricant is added to the mixture of (a) above prior to passing through a compactor. Suitable lubricants include stearic acid (e.g. magnesium stearate), colloidal silica and talc.

In yet another aspect, the resulting pharmaceutical composition is tabletted. In an alternative aspect of the invention, the lubricant (such as magnesium stearate) can be added to the dry granules prior to milling, and then the resulting pharmaceutical composition is milled and then tabletted.

In another aspect, this invention provides a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the roller compaction formulation comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the roller compaction formulation comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the roller compaction formulation comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the roller compaction formulation comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the roller compaction formulation contains 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the roller compaction formulation contains 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the roller compaction formulation comprises less than or equal to 30% w/w of one or more effervescent agents.

In a further aspect, the roller compaction formulation comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the roller compaction formulation comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the roller compaction formulation comprises less than or equal to 10% w/w of one or more effervescent agents.

In a yet further aspect, the roller compaction formulation comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of an effervescent; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the roller compaction formulation comprises Formula (I) and/or hydrate thereof, one or more effervescent agents, filler(s), binding agent(s), lubricant(s) and disintegrant(s).

In a still further embodiment of the invention, the roller compaction formulation does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or a hydrate thereof.

In another aspect, this invention provides a tablet formed by compressing the roller compaction formulation.

In a further aspect of the invention there is provided a process for the manufacture of a pharmaceutical composition which process (direct compression process) comprises:

(a) blending Formula (I) and/or hydrate thereof with one or more effervescent agents, one or more fillers (such as mannitol) and optionally in the presence of one or more binding agents and/or one or more disintegrants and/or one or more lubricants and/or one or more other excipients;

(b) compressing the mixture of (a) above.

In another aspect of the invention the direct compression formulation comprises Formula (I) and/or hydrate thereof, one or more effervescent agents, filler(s), binding agent(s), lubricant(s) and disintegrant(s).

In another aspect, this invention provides a tablet formed directly by compressing the mixture of (a) above.

In another aspect, this invention provides a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the direct compression formulation comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the direct compression formulation comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the direct compression formulation comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the direct compression formulation comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the direct compression formulation contains 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the direct compression formulation contains 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the direct compression formulation comprises less than or equal to 30% w/w of one or more effervescent agents.

In a further aspect, the direct compression formulation comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the direct compression formulation comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the direct compression formulation comprises less than or equal to 10% w/w of one or more effervescent agents.

In a yet further aspect, the direct compression formulation comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further embodiment of the invention, the direct compression formulation does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or a hydrate thereof.

The pharmaceutical composition and/or tablet and/or wet granulation formulation and/or roller compaction formulation and/or direct compression formulation can additionally and optionally include a colourant, as long as it is approved and certified by the FDA. For example, exemplary colours include allura red, acid fuschin D, napthalone red B, food orange 8, eosin Y, phloxine B, erythrosine, natural red 4, carmine, red iron oxide, yellow iron oxide, black iron oxide, titanium dioxide and the like.

Sweetening agents can also be added to the pharmaceutical composition and/or tablet and/or wet granulation formulation and/or roller compaction formulation and/or direct compression formulation or to the outer core of the tablet to create or add to the sweetness. Saccharide fillers and binders, e.g. mannitol, lactose, and the like, can add to this effect. For example, cyclamates, saccharin, aspartame, acesulfame K (Mukherjee (1997) Food Chem. Toxicol. 35:1177-1179), or the like (Rolls (1991) Am. J. Clin. Nutr. 53:872-878), can be used. Sweeteners other than sugars have the advantage of reducing the bulk volume of the pharmaceutical composition and/or tablet (core tablet and/or coat) and/or wet granulation formulation and/or roller compaction formulation and/or direct compression formulation and not affecting the physical properties of the tablet.

It will be understood by the skilled person that the incorporation of one or more effervescent agents into the pharmaceutical composition may necessitate the use of appropriate packaging. In a further aspect of the invention, there is provided packaging suitable for a pharmaceutical composition wherein the pharmaceutical composition comprises one or more effervescent agents. Examples of such packaging include packaging providing moisture protection. Examples of such packaging include for example PVC packaging, PVC/PVDC packaging, PVC/CTFE packaging, OPA/aluminium/PVC packaging, aluminium packaging or aluminium blister packaging. Further examples of such packaging include bottles with or without desiccants.

Compounds of the invention can be used to treat or prevent autoimmune diseases and/or symptoms of such diseases and are expected to be useful as a therapeutic and prophylactic agent for diseases associated with an abnormal immune response (e.g. autoimmune diseases and allergic diseases) and various infections and cancers which are required for activation of an immune response. For example, compounds of the invention may be administered to a mammal, including man, for the treatment of the following non-limiting examples of autoimmune conditions or diseases: rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome. Compounds of the invention may be administered to a mammal, including man, for the treatment of the following non-limiting examples of cancers: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumours and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes.

According to a further feature of the present invention there is provided a method for treating an autoimmune disease state

in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) and/or a hydrate thereof.

The invention also provides a compound of Formula (I) and/or a hydrate thereof, for use in therapy.

In another aspect the invention provides the use of a compound of Formula (I) and/or a hydrate thereof in the manufacture of a medicament for use in therapy.

In a further aspect, there is provided a method for treating rheumatoid arthritis in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) and/or a hydrate thereof.

The invention also provides a compound of Formula (I) and/or a hydrate thereof, for use in the treatment of rheumatoid arthritis.

In another aspect the invention provides the use of a compound of Formula (I) and/or a hydrate thereof in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

In a further aspect, there is provided a method for treating systemic lupus erythematosus in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) and/or a hydrate thereof.

The invention also provides a compound of Formula (I) and/or a hydrate thereof, for use in the treatment of systemic lupus erythematosus.

In another aspect the invention provides the use of a compound of Formula (I) and/or a hydrate thereof in the manufacture of a medicament for use in the treatment of systemic lupus erythematosus.

In a further aspect, there is provided a method for treating cancer in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) and/or a hydrate thereof.

The invention also provides a compound of Formula (I) and/or a hydrate thereof, for use in the treatment of cancer.

In another aspect the invention provides the use of a compound of Formula (I) and/or a hydrate thereof in the manufacture of a medicament for use in the treatment of cancer.

Definitions

As used herein, the term "effervescent agent" refers to any pharmaceutically acceptable material which evolves a gas when placed in an aqueous environment, for example the evolution of carbon dioxide on acidification. An example of an effervescent agent is a carbonate, for example a metal carbonate (such as sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate or aluminium carbonate) or an organic carbonate (such as disodium glycine carbonate, dimethyl carbonate or ethylene carbonate). A further example of an effervescent agent is a bicarbonate, for example a metal bicarbonate (such as sodium hydrogen carbonate or potassium hydrogen carbonate). For the avoidance of doubt, each of the effervescent agents referred to above represents a separate and independent aspect of the invention.

In one particular aspect of the invention, the effervescent agent is selected from a carbonate or bicarbonate. In another particular aspect of the invention, the effervescent agent is selected from a metal carbonate or a metal bicarbonate. In another particular aspect of the invention, the effervescent agent is selected from sodium hydrogen carbonate, potassium hydrogen carbonate, magnesium carbonate or sodium carbonate. In a further particular aspect of the invention, the effervescent agent is sodium hydrogen carbonate.

For the avoidance of doubt, reference to either a % w/w or to a weight (in mgs) of "one or more effervescent agents" in any aspect of the invention refers to the combined total % w/w or the combined total weight (in mgs) of all effervescent agents. By way of example, a pharmaceutical composition comprising 10% w/w of sodium hydrogen carbonate and 10% w/w magnesium carbonate would comprise 20% w/w of "one or more effervescent agents".

As used herein, the term "binding agent" refers to a pharmaceutically acceptable compound or composition added to a formulation to hold the active pharmaceutical ingredient and inactive ingredients together in a cohesive mix. Dry binders used for direct compaction must exhibit cohesive and adhesive forces so that when compacted the particles agglomerate. Binders used for wet granulation are hydrophilic and soluble in water and are usually dissolved in water to form a wet mass that is then granulated. Examples of suitable binding agents includes, but are not limited to, Povidone, Plasdone K29/32, Plasdone S-630, hydropropyl cellulose, methylcellulose, polyvinylpyrrolidone, aluminium stearate, hydroxypropylmethylcellulose and the like. It is possible for such binding agents to additionally act as water sequestering agents (e.g. Povidone).

As used herein, the term "filler" refers to any pharmaceutically acceptable material or composition added to a formulation to add bulk. Suitable fillers include, but are not limited to, mannitol, lactose, microcrystalline cellulose, silified microcrystalline cellulose and dicalcium phosphate.

As used herein, the term "lubricant" refers to any pharmaceutically acceptable agent which reduces surface friction, lubricates the surface of the granule, decreases tendency to build-up of static electricity, and/or reduces friability of the granules. Thus, lubricants can serve as anti-agglomeration agents. Examples of suitable lubricants are magnesium stearate, stearic acid, sodium stearyl fumarate, colloidal silica, talc, other hydrogenated vegetable oil or triglycerides.

As used herein, the term "disintegrant" refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Examples of disintegrants include, but are not limited to, non-saccharide water soluble polymers, such as cross-linked povidine. Other disintegrants that can also be used include, e.g. croscarmellose sodium, sodium starch glycolate, and the like, e.g. see Khattab (1992) J. Pharm. Pharmacol. 45:687-691.

The term "drying" and "dried" refer to a process which decreases the water content of a composition to a desired level.

The terms "compressing", "molding" and "pressing" refer to the process of applying compressive force to a formulation (powder or granules), as within a die, to form a tablet. The terms "compressed tablet" and "pressed tablet" mean any tablet formed by such a process.

The term "tablet" is used in its common context, and refers to a solid composition made by compressing and/or molding a mixture of compositions in a form convenient for swallowing or application to any body cavity.

As used herein, "tablet strength" is the equivalent mass of the free acid form of Compound I based on the amount of Formula (II) present in the tablet. Thus by way of example, a tablet strength of 50 mg will contain about 63 mg of Formula (II).

As used herein, "percent loading" is calculated by reference to the amount of Formula (II).

The term "low pH" refers to a measured pH of less than 5, such as less than 3, for example between 0 and 3.

The term "satisfactory in vitro dissolution" refers to a percent dissolution of greater than or equal to 70% within 30 minutes in 0.1N hydrochloric acid solution at 37° C.+0.5° C. as measured using the general procedure of the United States Pharmacopeia (Apparatus 2).

Dissolution Performance of the Existing Tablet

Reference Table 1 shows the composition of the tablet of Formula (II) with a tablet strength of 50 mg (the 50 mg tablet) as currently administered in ongoing clinical trials together with an equivalent tablet of Formula (II) with a tablet strength of 100 mg (the 100 mg tablet). The tablets were prepared in accordance with WO2009/061909.

Tablet strength is the equivalent mass of the free acid form of Compound I based on the amount of Formula (II) present in the tablet. Thus by way of example, a tablet strength of 50 mg will contain about 63 mg of Formula (II). The percent loading of Formula (II) in the 50 mg tablet is 12.5% whereas the percent loading of Formula (II) in the 100 mg tablet is 25%.

REFERENCE TABLE 1

Material	50 mg tablet (% w/w)	100 mg tablet (% w/w)
Formula (II)	12.5	25.0
Pregelatinised starch	37.02	30.77
Sodium starch glycolate	5.77	5.77
Microcrystalline cellulose	37.02	30.77
Povidone	2.88	2.88
Magnesium stearate	0.96	0.96
Opadry II Blue 85F99003	3.85	3.85

Dissolution was determined according to the general procedure of the United States

Pharmacopeia using Apparatus 2 with 900 mL of 0.1N hydrochloric acid solution at 37° C.±0.5° C. and stirrer speed of 75 rpm. At 5, 15, 30, 45 and 60 minutes, 10 mL of dissolution solution was withdrawn and filtered through a 0.45 μM PTFE filter. The concentration of Formula (II) in solution was determined by uv spectroscopy (e.g. Agilent 8453) at a wavelength of 324 nm and path length of 2 mm against an external standard solution.

Table 2 shows the resulting tablet percent dissolution in 0.1N hydrochloric acid for the 50 mg reference tablet and for three separate batches of the 100 mg tablet having the reference formulation set forth in Table 1 after 30 minutes. A plot showing the dissolution profile over time is shown in FIG. **1**.

TABLE 2

Formulation Strength (mg)	Formula (II) (% w/w)	Mean % dissolution in 0.1N HCl at 30 minutes
50	12.5	87
100 - A	25	65
100 - B	25	41
100 - C	25	16

The 100 mg tablet exhibits unsatisfactory and/or variable dissolution performance (varying between 16% and 65%). This compares to the 50 mg tablet which exhibits satisfactory dissolution.

We have investigated a number of formulations where the percent loading of Formula (II) is 25% or greater, in a desire to increase the mean percent dissolution performance of a tablet which contains an increased percent loading of Formula (II). Mannitol, microcrystalline cellulose, silified microcrystalline cellulose, sodium chloride and di-sodium hydrogen phosphate, and individual combinations thereof, all failed to provide a percent dissolution in 0.1N hydrochloric acid after 30 minutes of greater than 50%. In addition, formulations which comprised citric acid, arginine, meglumine and Polyplasdone Crospovidine or combinations thereof also failed to provide satisfactory dissolution.

It was therefore surprising to find that formulations which contained an effervescent agent exhibited satisfactory dissolution, even where said formulations contained an increased percent loading of Formula (II) (e.g. 25% and/or 37.5%, and up to 50%).

Table 3 shows the selection of components for sixteen separate experiments to investigate dissolution in a tablet with an increased percent loading of Formula (II). The results are shown in FIG. **2**. Table 4 shows the selection of components for a further eight experiments and the results for these are shown in FIG. **3**. Tables 10 and 11 (in Example 6) show the selection of components for a further twelve experiments and the results for these are shown in FIG. **6**. In each case, all experiments which did not use an effervescent agent failed to achieve a percent dissolution in 0.1N hydrochloric acid after 30 minutes of greater than 50%. However, experiments which used an effervescent agent showed satisfactory dissolution. For the avoidance of doubt, the reference to water in Tables 3 and 4 refers to the amount of water added during the processing of the formulation and prior to any subsequent drying step. The composition of any final tablet form will not include the level of water indicated.

TABLE 3

Run	Formula (II) (% w/w)	Filler 1	Filler 2	Disintegrant (5% w/w)	SLS (% w/w)	MgSt (% w/w)	Water (% w/w)
1	25.0	Mannitol	Sodium Bicarbonate	SSG	0	1	15
2	25.0	Mannitol	MCC	CCS	0	1	35
3	37.5	SMCC	Sodium Bicarbonate	SSG	0	1	25
4	37.5	Mannitol	Sodium Bicarbonate	SSG	5	1	15
5	37.5	SMCC	MCC	CCS	0	1	55
6	37.5	SMCC	MCC	SSG	5	1	55
7	25.0	SMCC	MCC	CCS	5	1	55
8	25.0	Mannitol	MCC	SSG	5	1	35
9	25.0	SMCC	Sodium Bicarbonate	CCS	0	1	40

TABLE 3-continued

Run	Formula (II) (% w/w)	Filler 1	Filler 2	Disintegrant (5% w/w)	SLS (% w/w)	MgSt (% w/w)	Water (% w/w)
10	37.5	Mannitol	Sodium Bicarbonate	CCS	0	1	25
11	25.0	SMCC	MCC	SSG	0	1	55
12	37.5	Mannitol	MCC	SSG	0	1	30
13	37.5	SMCC	Sodium Bicarbonate	CCS	5	1	30
14	25.0	SMCC	Sodium Bicarbonate	SSG	5	1	30
15	37.5	Mannitol	MCC	CCS	5	1	35
16	25.0	Mannitol	Sodium Bicarbonate	CCS	5	1	15

TABLE 4

Run	Cmpd I (% w/w)	MCC (% w/w)	Filler 1	Filler 1 (% w/w)	PVP (% w/w)	SSG (% w/w)	MgSt (% w/w)	Mannitol (% w/w)	Water (% w/w)
1	37.9	15	disodium hydrogen phosphate	30	3	5	1.5	7.1	22.5
2	37.9	0	disodium hydrogen phosphate	10	3	5	1.5	42.1	20
3	37.9	0	sodium hydrogen carbonate	30	3	5	1.5	22.1	15
4	25.2	0	disodium hydrogen phosphate	10	3	5	1.5	54.8	17.5
5	25.2	0	disodium hydrogen phosphate	30	3	5	1.5	34.8	25
6	25.2	15	disodium hydrogen phosphate	10	3	5	1.5	39.8	25
7	25.2	15	sodium hydrogen carbonate	30	3	5	1.5	19.8	18.3
8	37.9	15	sodium hydrogen carbonate	10	3	5	1.5	27.1	26.7

Whilst we do not wish to be limited by theoretical considerations, the addition of an effervescent agent (such as sodium hydrogen carbonate) appears to change the disintegration mechanism from a swelling disintegration mechanism, wherein high drug loading prevents rapid hydration/swelling events and consequently leads to slower disintegrating tablets which only dissolves slowly, to an erosion dissolution mechanism. In particular, it is thought that incorporation of an effervescent agent (such as sodium hydrogen carbonate) allows the tablet to rapidly disintegrate (break) into small particles which dissolve quickly.

Manufacturing Process

The particular manufacturing process of this invention for wet granulation formulations comprises premixing all of the required formulation components except water and lubricant (s). In one preferred aspect, premixing is conducted in a mixer-granulator such as a PMA25, and premixing comprises mixing the components together at impeller speeds ranging between about 50 to about 500 rpm for a period of between about 2 to about 20 minutes. In another preferred aspect, batches were dry-blended for 4 minutes at 440 rpm with a chopper speed of 1500 rpm using a Diosna granulator P1/6.

Water is then sprayed onto/into the dry composition to form a wet granulation formulation described herein. The water is added at for example a constant rate over a period of for example from about 0.05 kg/min to about 1.0 kg/min with either constant mixing during addition or mixing after addition. In either event, mixing is continued until the wet granulation composition is homogenous. In an alternative aspect, water is added at a rate of 15 mL/min to a total volume of 8-12% (w/w).

The wet granulation formulation is then dried using conventional techniques to reduce water to a predetermined level. In one aspect, the water content of the dried granulated formulation is less than about 10% (for example about 5%) by weight. Drying can be conducted at various temperatures and times. One skilled in the art could readily determine the appropriate drying times based on the initial water content, the desired final water content, and the drying temperature(s) employed.

The particular manufacturing process of this invention for roller compaction formulations comprises preblending all of the required formulation components until homogenous. In one preferred aspect, preblending is conducted in a blender-granulator such as a Copley Mobile Blender, and preblending comprises mixing the components together at speeds ranging between about 50 to about 500 rpm for a period of between about 2 to about 20 minutes.

The homogenous mix is then passed through a roller compactor, such as an Alexanderwerk WP120 to produce dry granules.

The dried granulated formulation produced via the wet granulation and/or roller compaction process is milled using conventional techniques and machinery. In one aspect, the formulation is milled through an appropriate mesh screen using commercially available milling equipment such as, e.g. Quadro Comil.

Following milling, the lubricant(s) (for example magnesium stearate) is added to the granulated formulation which is then blended using conventional techniques and machinery. Alternatively, the lubricant(s) (such as magnesium stearate) can be added to the dry granules prior to milling.

The pressing or compressing of the dried, granulated, milled and blended formulation can be accomplished using any tablet press. Many alternative means to effect this step are available, and the invention is not limited by the use of any particular equipment. In one aspect, the compression step is carried out using a Piccola Riva PV tablet press. In another aspect, the compression step is carried out by using an F3 Manesty press.

The diameter and shape of the tablet depends upon the die and punches selected for the compression of the milled and mixed formulation. Tablets can be discoid, oval, oblong, round, cylindrical, triangular, and the like. The tablets may be scored to facilitate breaking. The top or lower surface can be embossed or debossed with symbols or letters.

The compression force can be selected based on the type/model of press, a desired hardness of the resulting tabets, as well as other attributes such as friability, disintegration or dissolution characteristics, etc.

The particular manufacturing process of this invention for direct compression formulations comprises preblending all of the required formulation components. In one preferred aspect, all of the required formulation components except lubricant(s) are mixed in a mixer-granulator (such as a PMA25 at impeller speeds ranging between about 50 to about 500 rpm for a period of between about 2 to about 20 minutes), and thereafter lubricant(s) added and the resulting mixture blended (using for example a WAB turbula at speeds ranging between about 50 to about 500 rpm for a period of between about 2 to about 20 minutes). The resulting mixture is then compressed into tablet core using conventional techniques.

DESCRIPTION OF FIGURES

FIG. **1** shows a plot of the percent dissolution in 0.1N hydrochloric acid of existing tablets of strength 50 mg and 100 mg versus time.

FIG. **2** shows a plot of the percent dissolution in 0.1N hydrochloric acid of sixteen alternative tablet forms versus time.

FIG. **3** shows a plot of the percent dissolution in 0.1N hydrochloric acid of a further eight alternative tablet forms versus time.

FIG. **4** shows a plot of the percent dissolution in 0.1N hydrochloric acid of eight tablet forms obtained via a roller compaction process versus time.

FIG. **5** shows a plot of the percent dissolution in 0.1N hydrochloric acid of a tablet form obtained via a direct compression process versus time.

FIG. **6** shows a plot of the percent dissolution in 0.1N hydrochloric acid of a further twelve alternative tablet forms versus time.

FIG. **7** shows a plot of weight loss versus time of five tablet forms after placing the tablets in 0.1 N HCl (run 1).

FIG. **8** shows a plot of weight loss versus time of five tablet forms after placing the tablets in 0.1 N HCl (run 2).

FIG. **9** shows a plot of weight loss versus time of five tablet forms after placing the tablets in 0.1 N HCl (run 3).

EXAMPLES

The invention is further understood by reference to the following examples, which are intended to be purely exemplary of the invention. The present invention is not limited in scope by the exemplified aspects, which are intended as illustrations of single aspects of the invention only. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications fall within the scope of the appended claims.

In the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

GMP=good manufacturing practice
LOD=loss on drying
mg=milligram
MgSt=magnesium stearate
min=minute
mL=milliliter
nm=nanometer
JP=Japanese Pharmacopeia 15th Edition, English Version (Society of Japanese Pharmacopoeia) 2006
PhEur=European Pharmacopoeia 6th Edition (Directorate for the Quality of Medicines of the Council of Europe) 2009
PTFE=polytetrafluoroethylene
PVP=polyvinylpyrrolidone
rpm=revolutions per minute
SLS=sodium lauryl sulphate
SSG=sodium starch glycolate
USP—NF=United States Pharmacopeia 31/National Formulary 26 (The United States Pharmacopeia Convention) 2008
uv=ultraviolet
w/w=weight for weight

Table 5 below shows materials used, pharmacopeial status, grade and supplier.

TABLE 5

Material	Pharmacopeia	Grade	Supplier
Mannitol	PhEur USP-NF JP	Pearlitol 160c Pearlitol 120c Parteck M200	Roquette Freres S.A. (France)
Cellulose, microcrystalline	PhEur USP-NF JP	Avicel ® PH-101 Avicel ® PH-102	FMC Biopolymer (Ireland)
Sodium chloride	Ph Eur BP JP USP	Emprove	Merck Chemicals Ltd (UK)
di-Sodium hydrogen phosphate	Ph Eur BP USP	Emprove	Merck Chemicals Ltd (UK)
Sodium hydrogen carbonate	Ph Eur BP JP USP	Emprove	Merck Chemicals Ltd (UK)
Sodium starch glycolate	Ph Eur USP-NF	Glycolys LV	Roquette Freres S.A. (France)
Croscarmellose sodium	Ph Eur USP JP	Ac-di-Sol	FMC Biopolymer (Ireland)

TABLE 5-continued

Material	Pharmacopeia	Grade	Supplier
Magnesium stearate	Ph Eur USP-NF JP	NF Non Bovine	Mallinckrodt (USA)
Povidone	Ph Eur USP	Kollidon 30 K29/32	BASF (Germany) ISP (Germany)
Sodium lauryl sulphate (Sodium dodecyl sulfate)	USP NF	N/A	Sigma Aldrich (UK)
Silified microcrystalline cellulose	Ph Eur JP NF	Prosolv 50	JRS Pharma (Germany)
Pre-gelatinised starch 1500	Ph Eur NF	Starch 1500	Colorcon (USA)
Colloidal silica	USP-NF	Aeorsil	Evonik (Germany)

Table 6 below shows equipment used, model and supplier.

TABLE 6

Make	Model	Supplier
Diosna	P1/6	Dierks & Söhne Gmbh, Osnabrück, Germany
Quadro	Comil U3 & Comil 194	Quadro Engineering, Waterloo, Canada
WAB	Turbula T2F	Willy A. Bachofen AG, Muttenz, Switzerland
Riva	Piccola Nova	RivaSA, Buenos Aires, Argentina
Aeromatic	Strea 1	Casburt Pharmaceutical Equipment, Stoke-on-Trent, UK
Alexanderwerk	WP 120	Alexanderwerk AG, Remscheid, Germany
Copley Mobile Blender	Mobile Blender	Copley Scientific, Nottingham, UK
Niro-Fielder	PMA25	Aeromatic Fielder, Eastleigh, UK
Fette	1200	Fette Compacting GmbH, Schwarzenbek, Germany
Aeromatic-Fielder	MP1	Aeromatic Fielder, Eastleigh, UK
Vector	MFL.01	Vector Corporation, Marion, IA, U.S.A
F3	Manesty	Manesty, Knowsley, UK

Example 1

Assessment of Dissolution Performance of Sixteen Alternative Tablet Forms

Sixteen different prototype tablets were prepared from a wet granulation formulation using methods well known to those skilled in the art. The composition of each of these tablets is set out in Table 3 above (not including water).

Formula (II) and the excipients described in Table 3 (total batch size approximately 250 g) are charged to a mixer-granulator (Diosna, 1 L) and mixed for 5 minutes at 300 rpm. Purified water (ranging from 15% w/w to 55% w/was set out in Table 3) is added to the powders with further mixing until a suitable wet mass is formed (ranging from 7 to 17 mins) at 300 rpm. The resultant granules are dried to appropriate moisture content (<6% LOD) using a fluid bed dryer (Vector) with an inlet air temperature of 60° C. The dried granules are milled using an appropriately sized screen (1 mm, Quadro Comil U3). Magnesium stearate is then added to the granules, which are then blended (WAB turbula) for 5 mins at 55 rpm before compressing into tablet cores using conventional tabletting equipment (F3 tablet press).

Dissolution was determined in accordance with the procedure outlined in the description above and the dissolution profiles are shown in FIG. **2**.

Example 2

Assessment of Dissolution Performance of a Further Eight Alternative Tablet Forms

A further eight different prototype tablets were prepared from a wet granulation formulation using methods well known to those skilled in the art. The composition of each of these tablets is set out in Table 4 above (not including water).

Formula (II) and the excipients described in Table 4 (total batch size approximately 600 g) are charged to a mixer-granulator (Diosna, 4 L) and mixed. Purified water (ranging from 15% w/w to 26.7% w/was set out in Table 4) is added to the powders with further mixing until a suitable wet mass is formed (ranging from 10 to 24 mins) at 200 rpm. The resultant granules are dried to appropriate moisture content (<5% LOD) using a fluid bed dryer (Aeromatic Strea) with an inlet air temperature of 100° C. The dried granules are milled using an appropriately sized screen (1 mm, Quadro Comil U3). Magnesium stearate is then added to the granules, which are then blended (WAB turbula) for 10 mins at 50 rpm before compressing into tablet cores using conventional tabletting equipment (Riva Piccola).

Dissolution was determined in accordance with the procedure outlined in the description above and the dissolution profiles are shown in FIG. **3**.

Example 3

Assessment of Dissolution Performance of Tablets of Formula (II) Prepared by Roller Compaction Process

Eight formulations selected from Examples 2 and 3 were assessed for feasibility in a roller compaction process using methods well known to those skilled in the art. The composition of each of these formulations is set out in Table 7 below. Formula (II) and the excipients described in Table 7 (total batch size approximately 1.5 kg) are charged to a mixer to produce a homogenous mix (Copley Mobile Blender) for 5 minutes at 30 rpm. The homogeneous mix is then passed through a roller compactor (Alexanderwerk, 40 mm roller size, 25 bar roller pressure, 2.5 rpm roller speed, 2.0 mm roller-gap size) to produce dry granules. The dry granules are then blended with magnesium stearate (Copley Mobile Blender). The resultant granules are compressed into tablet cores using conventional tabletting equipment (Riva Piccola).

TABLE 7

	Formulation (% w/w)							
Component	1	2	3	4	5	6	7	8
Formula (II)	37.9	25.2	37.9	37.9	37.9	37.9	37.9	37.9
Mannitol	22.1	54.8	27.1	27.1	45.1	45.1	42.1	45.1
(Silicified) Micro-crystalline cellulose	0	0	15	15	10	10	10	10
Sodium hydrogen carbonate	30	10	10	10	0	0	0	0
Povidone	3	3	3	3	0	0	3	0
Sodium Starch glycolate	5	5	5	5	5	5	5	5
Colloidal silica	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Intragranular Magnesuim Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

TABLE 7-continued

Component	Formulation (% w/w) 1	2	3	4	5	6	7	8
Extragranular Magnesuim Stearate	1	1	1	1	1	1	1	1

Formulations 1, 2, 3 and 8 were manufactured using Pearlitol 160 C. The remaining formulations used Parteck M200 mannitol. Formulations 3, 4, 6 and 7 used microcrystalline cellulose (Avicel PH101). Formulations 5 and 8 used silicified microcrystalline cellulose (Prosolv 50).

Dissolution was determined in accordance with the procedure outlined in the description above and the dissolution profiles are shown in FIG. **4**.

Example 4

Assessment of Dissolution Performance of Tablets of Formula (II) Prepared by Direct Compression

Tablets were prepared using direct compression formulation using methods well known to those skilled in the art. The composition of the tablets is as per Table 3, Run 9 above (without the addition of water).

Formula (II) and the excipients described in Table 3, Run 9 (total batch size approximately 250 g) are charged to a mixer-granulator (Diosna, 1 L) and mixed for 5 minutes at 300 rpm. Magnesium stearate is then added to the blend, which is then blended (WAB Turbula) for 5 minutes at 55 rpm before compressing into tablet cores using conventional tabletting equipment (F3 tablet press).

Dissolution was determined in accordance with the procedure outlined in the description above and the dissolution profiles are shown in FIG. **5**.

Example 5

Preparation of Tablets of Formula (II)

Tablets containing the components set out in Table 8 below were prepared using methods well known to those skilled in the art, in particular using conventional mixing, wet granulation, compression and film coating processes, according to GMP.

Formula (II), mannitol, sodium hydrogen carbonate, sodium starch glycolate and povidone are charged to a mixer-granulator (PMA25) and mixed. Purified water is added to the powders with further mixing until a suitable wet mass is formed. The wet mass may be passed through a screen to break up any large agglomerates. The resultant granules are dried to appropriate moisture content (<5% LOD) using a fluid bed dryer (MP1). The dried granules are milled using an appropriately sized screen (for example 1.1 mm, Comil 194). Magnesium stearate is then added to the granules, which are then blended (Copley) before compressing into tablet cores using conventional tabletting equipment (Fette 1200).

TABLE 8

Tablet strength Components	50 mg mg/tablet	100 mg mg/tablet	150 mg mg/tablet	Standard
Formula (II)	63.1	126.2	189.3	AstraZeneca
Mannitol	61.8	248.6	185.3	Ph Eur, NF, JP

TABLE 8-continued

Tablet strength Components	50 mg mg/tablet	100 mg mg/tablet	150 mg mg/tablet	Standard
Sodium hydrogen carbonate	25.0	75.0	74.9	Ph Eur, USP, JP
Sodium starch glycolate	8.3	25.0	25.0	Ph Eur, NF
Povidone	5.0	15.0	15.0	Ph Eur, USP, JP, NF
Magnesium stearate	3.3	10.0	10.0	Ph Eur, NF

Example 6

Assessment of Dissolution Performance of Additional Tablet Forms

Potassium hydrogen carbonate ($KHCO_3$), magnesium carbonate ($MgCO_3$) and sodium carbonate (Na_2CO_3) were incorporated into the tablet formulation in place of sodium hydrogen carbonate. The level of each was corrected to evolve the same quantity of carbon dioxide.

Sodium carbonate (Na_2CO_3) was incorporated at two concentrations to provide better understanding of the mechanism of action of these effervescent agents in the formulation. This took advantage of the fact that the reaction of sodium carbonate with hydrochloric acid takes place in two stages:

Stage I: sodium carbonate is converted to sodium hydrogen carbonate ($NaHCO_3$) as shown in the reaction:

$$Na_2CO_3+HCl\rightarrow NaHCO_3+NaCl$$

Stage 11: the gas, carbon dioxide is released

$$NaHCO_3+HCl\rightarrow NaCl+H_2O+CO_2$$

Accordingly, sodium carbonate has stronger alkalizing activity compared to sodium hydrogen carbonate due to its capability to accept two hydrogen ions but has slower effervescent activity as evolution of the gas (CO_2) requires two steps reaction to take place.

Therefore, two levels of sodium carbonate were investigated. The lower level (9.5%) gave similar alkalisation capacity to 15% sodium hydrogen carbonate but with a lower amount of CO_2 to evolve in acidic environment. The higher level (15%) evolved the same total amount of CO_2 as 15% sodium hydrogen carbonate but at slower rate and with higher alkalisation capacity.

In addition, arginine and meglumine were investigated as alternatives to sodium hydrogen carbonate. Arginine and meglumine provide alkalising activity without any effervescent activity.

Moreover, citric acid was incorporated in one formulation to provide acidity to the microenvironment of the tablets and counteract the alkalising effect of sodium hydrogen carbonate. The level of citric acid was adjusted to neutralise the alkalinity of sodium hydrogen carbonate.

Furthermore, incorporation of higher levels of Formula (II) in the formulation was included at two levels of sodium hydrogen carbonate, 15% and 25%, to address possible cor-

relation between the quantities of Formula (II) and the quantity of sodium hydrogen carbonate required to allow satisfactory dissolution.

Additionally, Polyplasdone® Crospovidone superdisintegrant was investigated in the formulation to replace sodium hydrogen carbonate and sodium starch glycolate in order to provide the possibility for rapid disintegration through a combination of swelling and wicking mechanism of disintegrations. Polyplasdone disintegrants are highly compressible materials and therefore higher level could be used to provide quicker disintegration. Polyplasdone® Crospovidone was investigated at two concentration 10% and 15%. Meglumine was included in these two formulations to provide high local pH (to prevent active pharmaceutical ingredient (API) gelling in acidic environment) and consequently offering a better opportunity to achieve complete dissolution in acid.

The formulation components and composition for each of the alternative tablet forms in Example 6 are presented in Tables 9, 10 and 11.

TABLE 9

Component	Supplier/Trade name	Function
Formula (II)	AstraZeneca/DSM Linz	Active Pharmaceutical Ingredient
Mannitol	Roquette Pearlitol 50C	Filler
sodium hydrogen carbonate (NaHCO3)	Merck Emprove	effervescent/ alkalizing agent
Potassium hydrogen carbonate (KHCO3)	Merck EMPROVE ® exp Ph Eur, BP, USP, FCC, E501	effervescent/ alkalizing agent
magnesium carbonate (MgCO3)	Merck Emprove, Heavy	effervescent/ alkalizing agent
sodium carbonate (Na2CO3)	Merck EMPROVE ® exp Ph Eur, BP, NF, anhydrous	effervescent/ alkalizing agent
Citric Acid	Merck EMPROVE ® exp Ph Eur, BP, JP, USP, E 330, FCC, anhydrous	Acidifying agent
L-arginine (Arg)	Merck EMPROVE ® exp Ph Eur, USP	alkalizing agent
Meglumine (Megl)	Merck EMPROVE ® api Ph Eur, JP, USP	alkalizing agent
Crospovidone (CrosPosv)	Polyplasdone ® Crospovidone	Disintegrant
Sodium Starch Glycolate (SSG)	Expltab	Disintegrant
Polyvinylpyrrolidone (PVP)	BASF Kollidon K30	Binder
Magnesium Stearate (MgSt)	Mallinkrodt non-bovine	Lubricant

Batches of drug substance and excipients were dispensed to form a total nominal batch size of 600 g (Table 11). Magnesium stearate was included in the nominal total but was not included during granulation. Following drying, magnesium stearate was added to make up 2% of the total dry granules.

A wet granulation process was used to prepare the granules for tabletting using the method below.

Batches were dry blended for 4 min at 440 rpm with chopper speed of 1500 rpm using Diosna granulator P1/6 (Dierks & Söhne Gmbh, Osnabruck, Germany) in the 4 L bowl.

Water was added drop wise at a rate of 15 mL.min-1 to a total volume of 8-12% (w/w). The endpoint was checked by passing a sample of powder through a 1 mm sieve and judging whether there were fines and whether most of the materials were granular.

The wet mass was dried using Niro-Aeromatic Strea fluid bed dryer (Casburt Pharmaceutical Equipment, Stoke-on-Trent, UK) with a maximum inlet temperature of 90° C. and an appropriate fluidizing airflow. Extent of drying was determined using a moisture analyser (Mettler Toledo HB43) to <2%.

The dried granular mass was milled at 3000 rpm through a 1.0 mm screen using a U3 bench top Quadro Comil mill (Quadro Engineering, Waterloo, Canada).

The lubricant was then added at level of 2% by weight of the dried mass of granules and was blended using a Turbula blender (Willy A. Bachofen A G, Muttenz, Switzerland) at 50 rpm for 15 min.

The resultant mixtures were compressed using an F3 Manesty press (Casburt Pharmaceutical Equipment, Stoke-on-Trent, UK). The target compression force was 14 kN as used during A23 [RITA.000-376-136]. The compression force was assessed using DAAS instrumentation (Waltti Electronics Ltd., Kuopio, Finland).

Batches were compressed using 11 mm round concave tooling. Tablets were compressed to a target weight of 500 mg. Some tablets were collected from the line to allow weight and hardness to be correlated with compression force.

The resultant tablets were de-dusted and kept in air tight plastic bottles for analysis.

TABLE 10

	Run											
	1	2	3	4	5	6	7	8	9	10	11a	11b
Formula (II) (%)	37.9	37.9	37.9	37.9	37.9	37.9	37.9	37.9	37.9	37.9	50	50
NaHCO3 (%)	15	0	0	15	0	0	0	0	0	0	15	25
Na2CO3 (%)	0	15	9.465	0	0	0	0	0	0	0	0	0
Citric acid (%)	0	0	0	34.305	0	0	0	0	0	0	0	0
KHCO3 (%)	0	0	0	0	17.88	0	0	0	0	0	0	0
MgCO3 (%)	0	0	0	0	0	15.06	0	0	0	0	0	0
Arg (%)	0	0	0	0	0	0	31.1	0	0	0	0	0
Megl (%)	0	0	0	0	0	0	0	34.86	34.86	34.86	0	0
CrosPove (%)	0	0	0	0	0	0	0	0	10	15	0	0
SSG (%)	5	5	5	5	5	5	5	5	0	0	5	5
PVP (%)	3	3	3	3	3	3	3	3	3	3	3	3
MgSt (%)	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol (%)	37.1	37.1	42.64	2.795	34.22	37.04	20.99	17.24	12.24	7.24	25	15

TABLE 11

	1	2	3	4	5	6	7	8	9	10	11a	11b
Formula (II) (g)	227.4	227.4	227.4	227.4	227.4	227.4	227.4	227.4	227.4	227.4	300	300
NaHCO3 (g)	90	0	0	90	0	0	0	0	0	0	90	150
Na2CO3 (g)	0	90	56.79	0	0	0	0	0	0	0	0	0
Citric acid (g)	0	0	0	205.83	0	0	0	0	0	0	0	0
KHCO3 (g)	0	0	0	0	107.28	0	0	0	0	0	0	0
MgCO3 (g)	0	0	0	0	0	90.36	0	0	0	0	0	0
Arg (g)	0	0	0	0	0	0	186.66	0	0	0	0	0
Megl (g)	0	0	0	0	0	0	0	209.16	209.16	209.16	0	0
CrosPove (g)	0	0	0	0	0	0	0	0	60	90	0	0
SSG (g)	30	30	30	30	30	30	30	30	0	0	30	30
PVP (g)	18	18	18	18	18	18	18	18	18	18	18	18
MgSt (g)	12	12	12	12	12	12	12	12	12	12	12	12
Mannitol (g)	222.6	222.6	255.8	16.77	205.3	222.2	125.9	103.4	73.44	43.44	150	90

Disintegration time was measured using an Erweka Copley ZT74 disintegration machine. The experiment was carried out at 36-38° C. using 0.7 L tap water and the disc method. Six tablets were tested for each batch. Results are presented as mean±SD (n=6).

Sotax HT100 was used to determine the weight, hardness, thickness and diameter of 15 tablets from each batch. The Sotax is an automated tablet tester, which measures each parameter at a different station for a specified number of tablets using a specific method ("11 mm 500 mg Round Uncoated n15"). First the weight is measured, then the tablet is passed to a thickness gauge before being passed to a jaw where the diameter and hardness are measured. A report is then generated with individual data for each of the tablets tested, as well as the calculated mean and RSD for each batch. Results are presented as mean±SD (n=15).

The true density of the tablets was obtained by helium pycnometry using the AccuPyc. Ten tablets were weighed accurately, placed in the sample cup previously used for calibration and analysed. True density was calculated for each batch using the equation set out below and was found to be between 1.55 and 1.56 g/cc for each of them.

$$\text{True density} = (\text{mass/volume of solids})$$

Tablet envelope density (apparent density) was then obtained by a volume displacement method using the GeoPyc. The same ten tablets were then placed in the 25.4 cm cylinder with DryFlo. The porosity was calculated by the GeoPyc using the true density data from above and the following equation:

$$\text{Apparent density} = (\text{mass of tablets/envelope volume of tablets})$$

The porosity of the tablets was then determined using the apparent density and true density calculated above in the following equation:

$$\text{Porosity} = 100 \times 1 - (\text{apparent density/true density})$$

Dissolution was determined in accordance with the procedure outlined in the description above.

The amount of gas evolved as a result of the tablets being placed in an acidic environment was assessed. A 250 ml beaker filled with 100 ml of 0.1 N HCl (pH 1) was placed over a balance connected to a PC to transmit the weight at regular time interval (every 15 seconds). The balance was left to settle until the balance reading was stable. One tablet was dropped in the beaker and weight recording was started. The weight difference was calculated and plotted as a function of time.

Weight, hardness, disintegration time and porosity data are summarised in Table 12.

TABLE 12

	Weight (mg)		Hardness (kp)		Disintegration time (s)		Porosity (%)	
	Average	SD	Average	SD	Average	SD	Average	SD
1	500.3	5.00	9	0.9	327.5	25.03	13.10	0.39
2	501.6	10.43	9	2.4	475.5	43.72	15.43	0.37
3	476.3	15.86	7	2.7	426.16	39.42	13.90	0.23
5	505.4	3.08	9	0.7	454	23.41	12.66	0.33
6	487.2	13.03	10	2	134	9.01	15.99	0.06
7	493	19.53	8	2.7	338	10.12	14.62	0.29
8	491.1	26.68	11	3.1	360.0	26.50	10.33	0.10
9	509.2	6.17	15	1.7	367.0	97.6	9.18	0.14
10	499.1	7.72	9	1.1	516.7	15.2	14.66	0.14
11a	504.4	12.29	9	2.2	461.3	19.2	14.19	0.05
11b	499.4	16.9	9	2	487.2	56.4	12.66	0.17

The dissolution profiles of the tablets in 0.1 M HCl are presented in FIG. **6**. No result is given for Run 4 as no satisfactory formulation could be achieved and therefore no dissolution measurement was taken.

Results from gas evolution quantification are presented in FIGS. **7**, **8** and **9**.

The results showed that alkalising agents which did not additionally provide effervescent activity failed to provide tablets of Formula (II) which gave satisfactory dissolution. The results suggest that effervescent agents such as sodium hydrogen carbonate, potassium hydrogen carbonate and magnesium carbonate enhance the dissolution of the tablet.

The tablet with a lower level of sodium carbonate provided a lower level of dissolution compared to the tablet with a higher level of sodium carbonate. Furthermore, the tablet with the higher level of sodium carbonate provided dissolution at a lower rate and extent compared to tablets with sodium hydrogen carbonate. This could be explained as a result of slower carbon dioxide evolution.

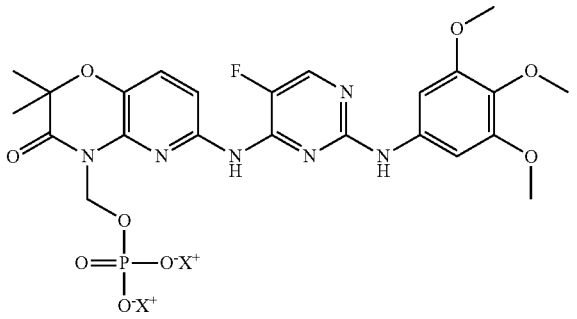
Accordingly, the rate and extent of carbon dioxide evolution appear to effect the dissolution profile of the tablet.

The results further show that increased drug loading (for example greater than or equal to 50% w/w of Formula (II)) exhibiting a satisfactory dissolution profile can be achieved using sodium hydrogen carbonate. Furthermore, the results show that higher levels of sodium hydrogen carbonate (greater than or equal to 25%) were not necessary to achieve a satisfactory dissolution profile.

The invention claimed is:

1. A solid pharmaceutical composition comprising greater than 15% w/w of the compound of Formula (I):

Formula (I)



wherein each X^+ represents a monovalent cation;

and/or a hydrate thereof;

and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution at low pH;

and further comprising one or more pharmaceutically acceptable ingredients.

2. The solid pharmaceutical composition according to claim **1** comprising greater than or equal to 25% w/w of the compound of Formula (I) and/or hydrate thereof.

3. The solid pharmaceutical composition according to claim **1** comprising less than or equal to 20% w/w of the effervescent agent.

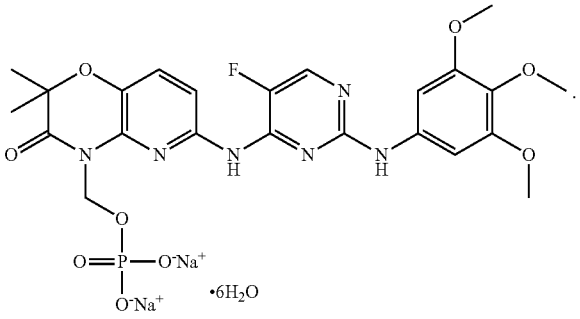
4. The solid pharmaceutical composition according to claim **1** wherein the effervescent agent is sodium hydrogen carbonate.

5. The solid pharmaceutical composition according to claim **1** wherein each X^+ in the compound of Formula (I) represents a sodium cation (Na^+).

6. The solid pharmaceutical composition according to claim **1** wherein the compound of Formula (I) is in the form of an hexahydrate.

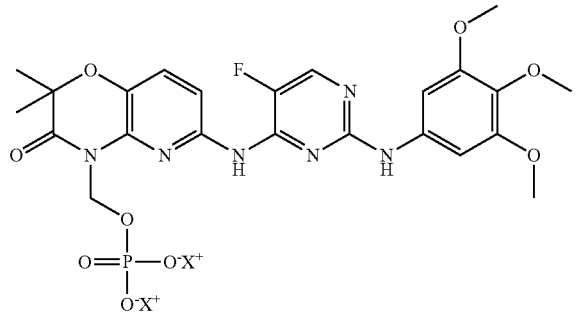
7. The solid pharmaceutical composition according to claim **1** wherein the compound of Formula (I) is in the form of Formula (II):

Formula (II)



8. A unit dosage form comprising greater than or equal to 60 mg of the compound of Formula (I):

Formula (I)



wherein each X^+ represents a monovalent cation; and/or a hydrate thereof;

and less than or equal to 110 mg of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution at low pH;

and further comprising one or more pharmaceutically acceptable ingredients.

* * * * *

EXHIBIT E

US008951504B2

(12) **United States Patent**
Gururajan et al.

(10) **Patent No.: US 8,951,504 B2**
(45) **Date of Patent: Feb. 10, 2015**

(54) **(TRIMETHOXYPHENYLAMINO) PYRIMIDINYL FORMULATIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/290,494**

(22) Filed: **May 29, 2014**

(65) **Prior Publication Data**

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(60) Provisional application No. 61/512,621, filed on Jul. 28, 2011.

(51) **Int. Cl.**

A61K 9/00	(2006.01)
A61K 9/46	(2006.01)
A61K 31/5383	(2006.01)
A61K 31/675	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/0007*** (2013.01); ***A61K 31/5383*** (2013.01); ***A61K 31/675*** (2013.01)

USPC **424/43**

(58) **Field of Classification Search**

None

See application file for complete search history.

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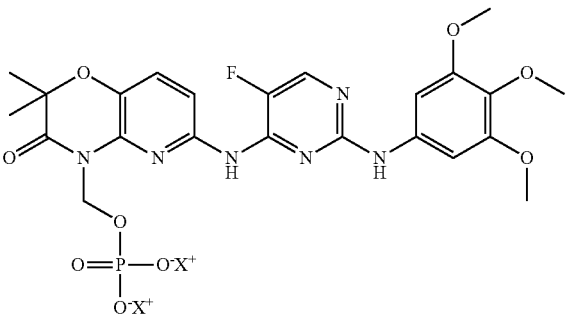
Assistant Examiner — Olga V Tcherkasskaya
(74) *Attorney, Agent, or Firm* — Travis Young; McDonnell Boehnen Hulbert & Berghoff LLP

(57) **ABSTRACT**

There are provided pharmaceutical compositions comprising greater than 15% w/w of a compound of Formula (I) as defined herein and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients; and to processes for obtaining them.

Formula (I)



24 Claims, 9 Drawing Sheets

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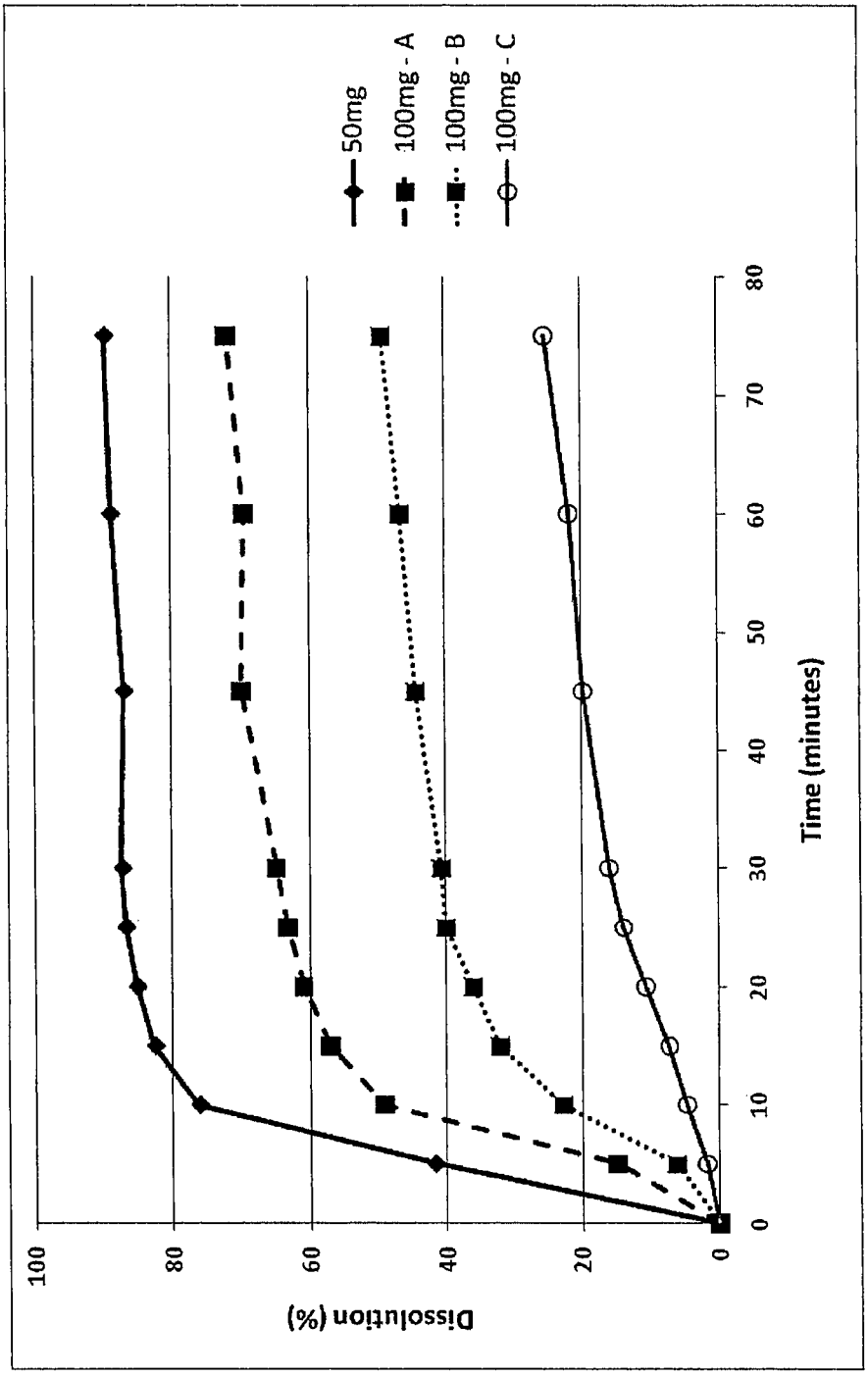

50mg
100mg - A
100mg - B
100mg - C
Dissolution (%)
0
20
40
60
80
100
Time (minutes)
0
10
20
30
40
50
60
70
80

Figure 1

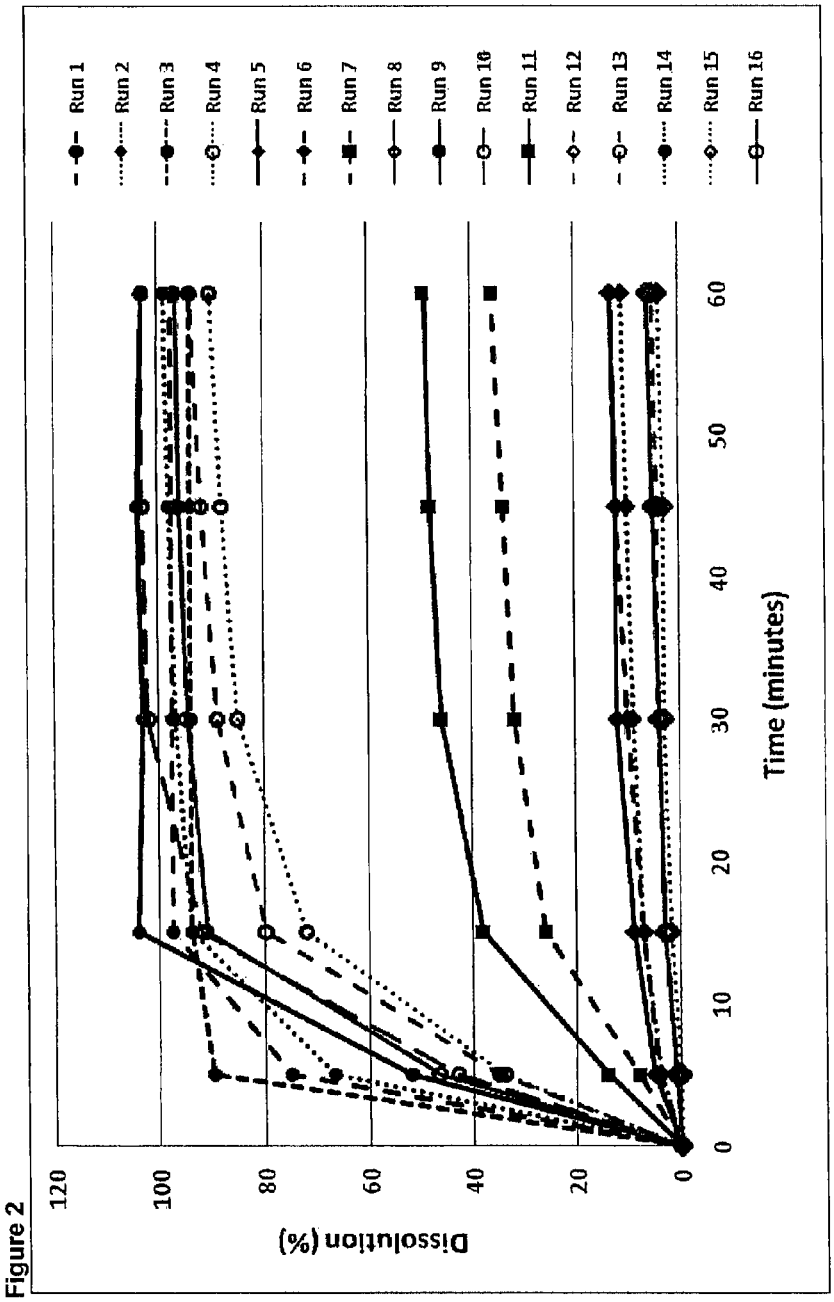

Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9
Run 10
Run 11
Run 12
Run 13
Run 14
Run 15
Run 16
Dissolution (%)
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minutes)
Key:
●○ Satisfactory dissolution – runs 1, 3, 4, 9, 10, 13, 14, 16
■ Low dissolution – runs 7, 11
◆◇Very low dissolution – runs 2, 5, 6, 8, 12, 15

Figure 2

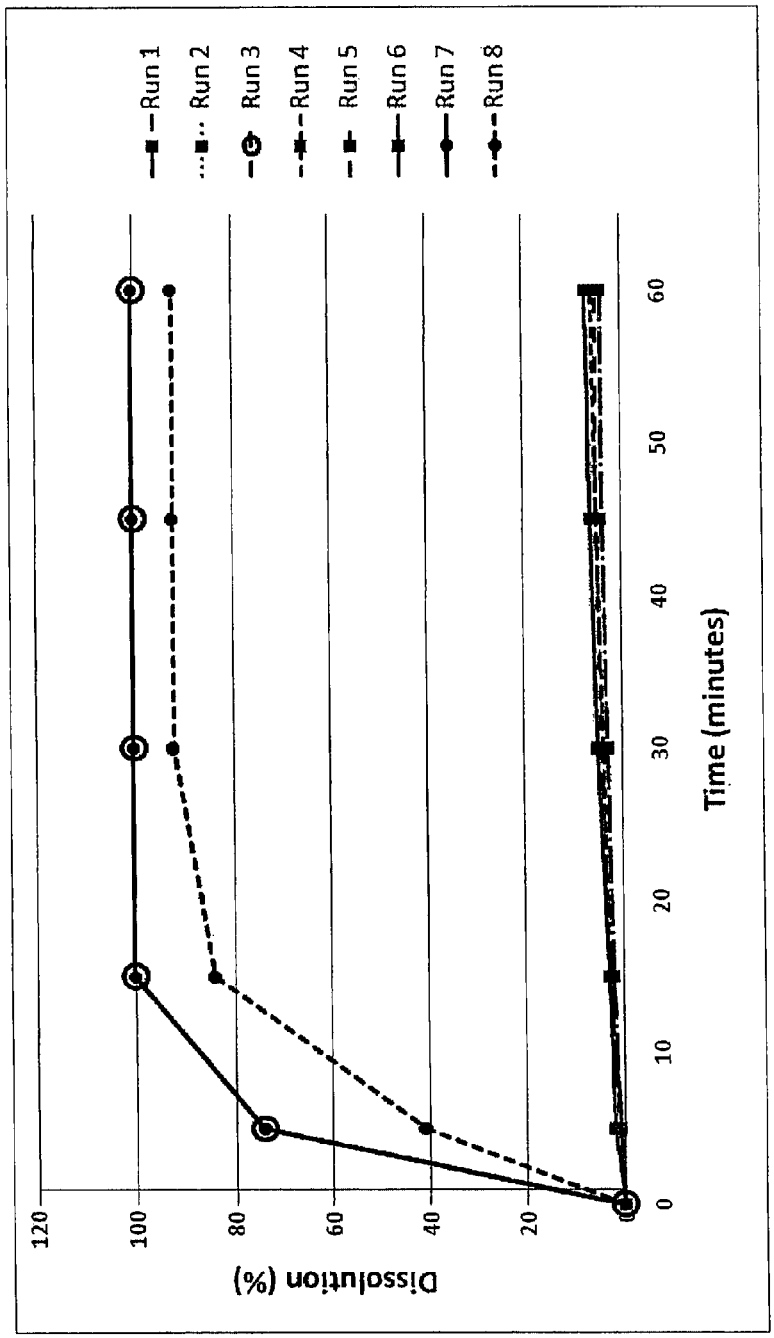

Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Dissolution (%)
120
100
80
60
40
20
0
Time (minutes)
0
10
20
30
40
50
60
Key:
●○ Satisfactory dissolution – runs 3,7,8
■ Low dissolution – runs 1,2,4,5,6

Figure 3

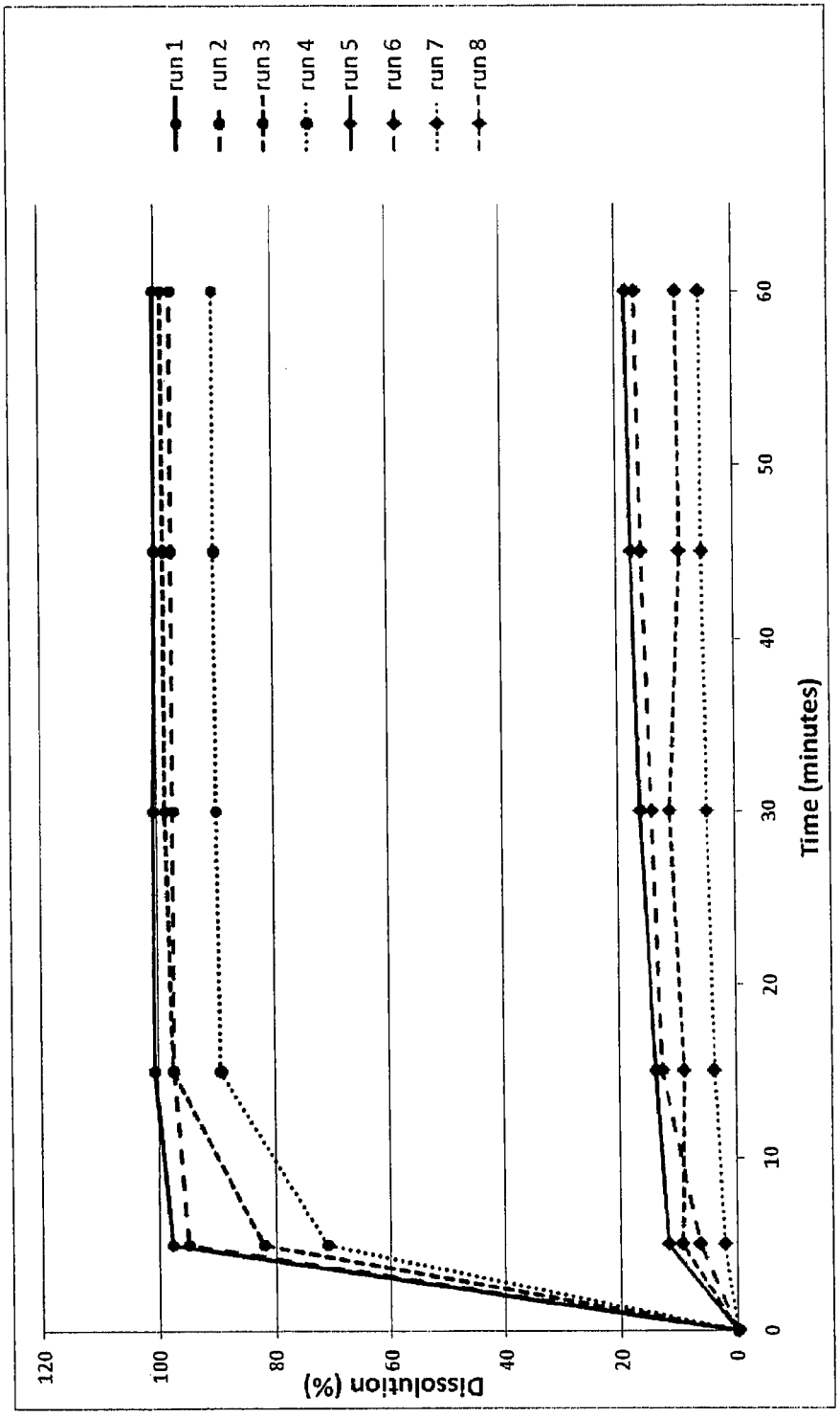

run 1
run 2
run 3
run 4
run 5
run 6
run 7
run 8
Dissolution (%)
120
100
80
60
40
20
0
Time (minutes)
0
10
20
30
40
50
60
Key:
● Satisfactory dissolution – runs 1, 2, 3, 4
◆ Low dissolution – runs 5, 6, 7, 8

Figure 4

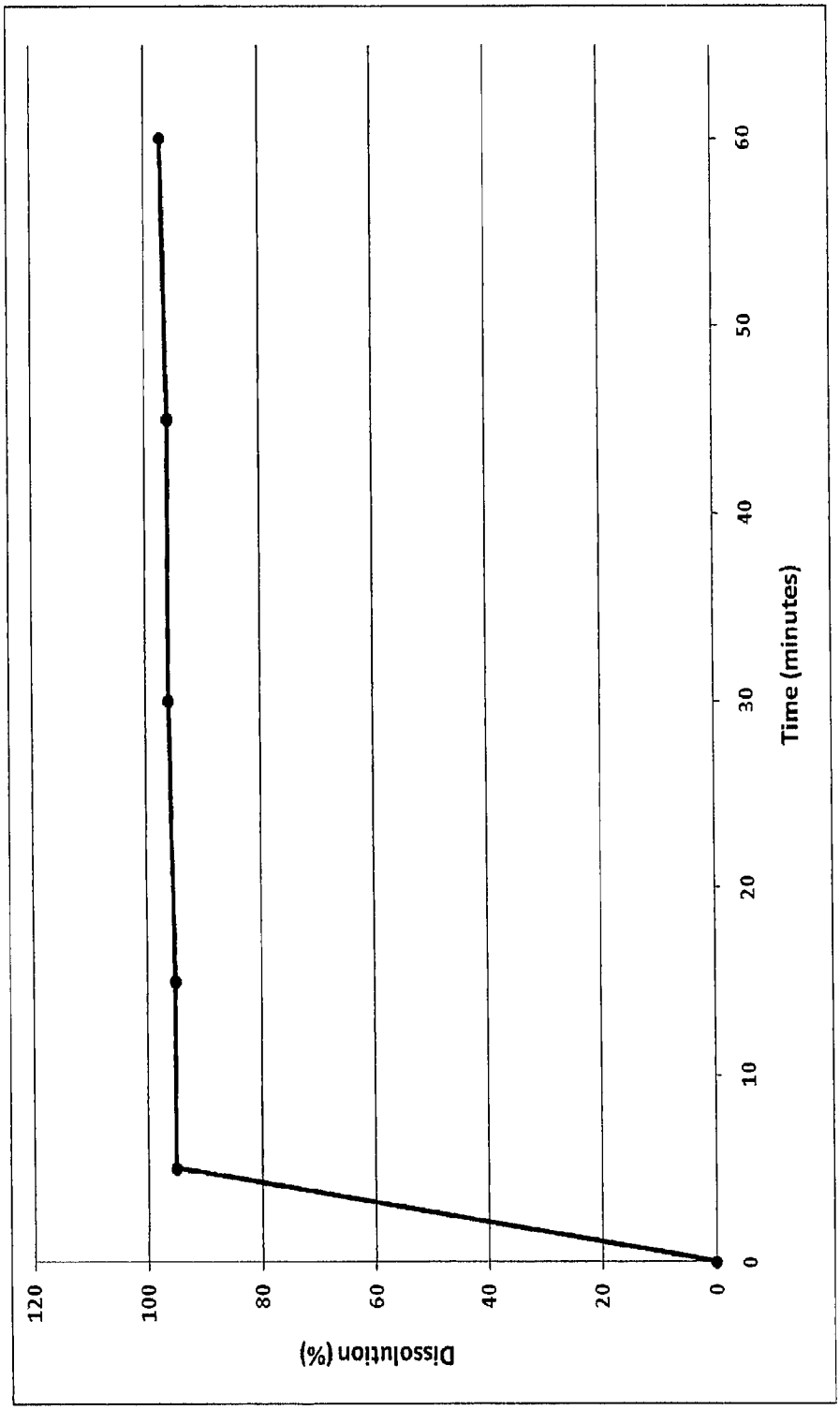

Dissolution (%)
120
100
80
60
40
20
0
Time (minutes)
0
10
20
30
40
50
60

Figure 5

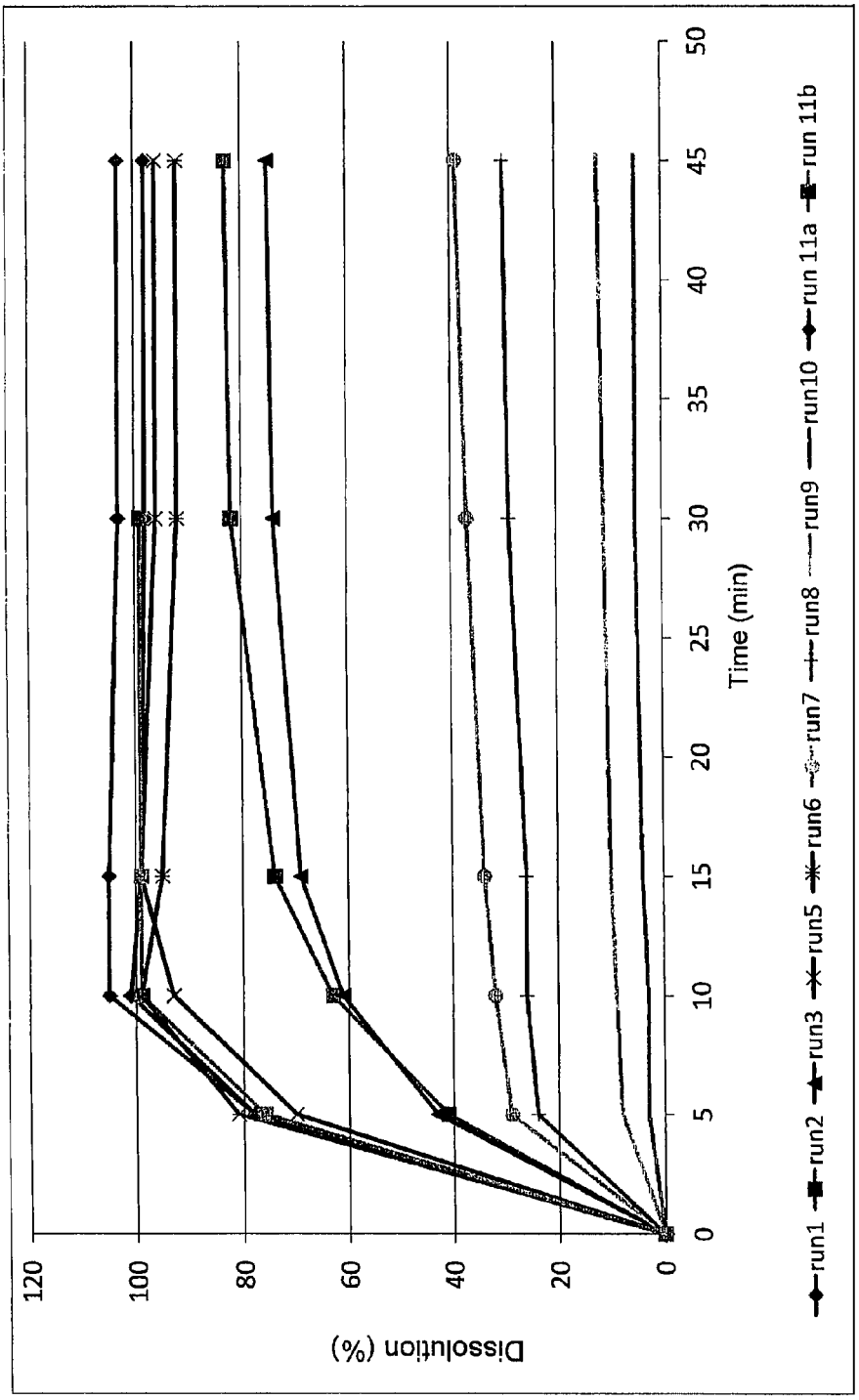

Dissolution (%)
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
50
Time (min)
run1
run2
run3
run5
run6
run7
run8
run9
run10
run 11a
run 11b

Figure 6

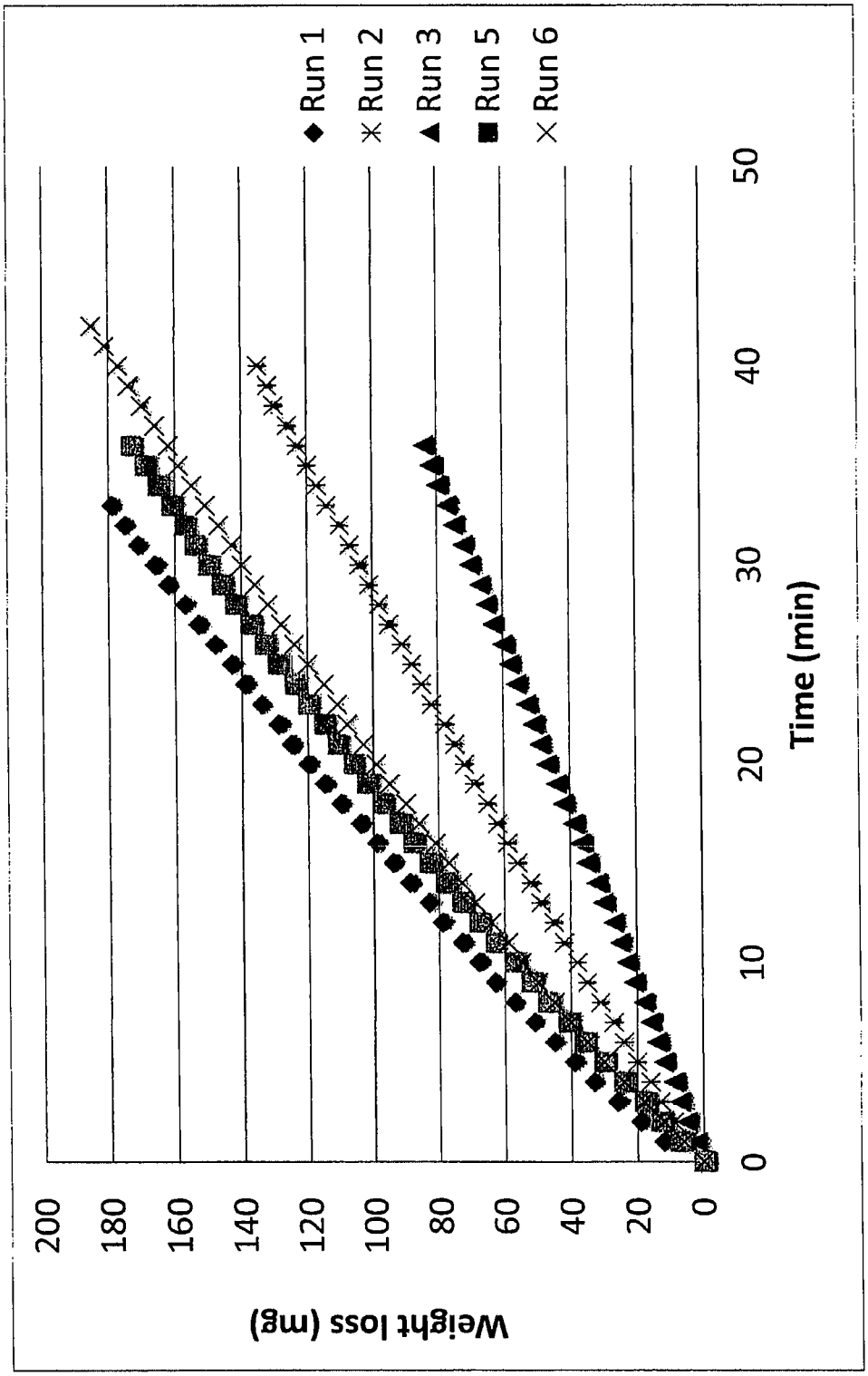

Run 1
Run 2
Run 3
Run 5
Run 6
Weight loss (mg)
0
20
40
60
80
100
120
140
160
180
200
Time (min)
0
10
20
30
40
50

Figure 7

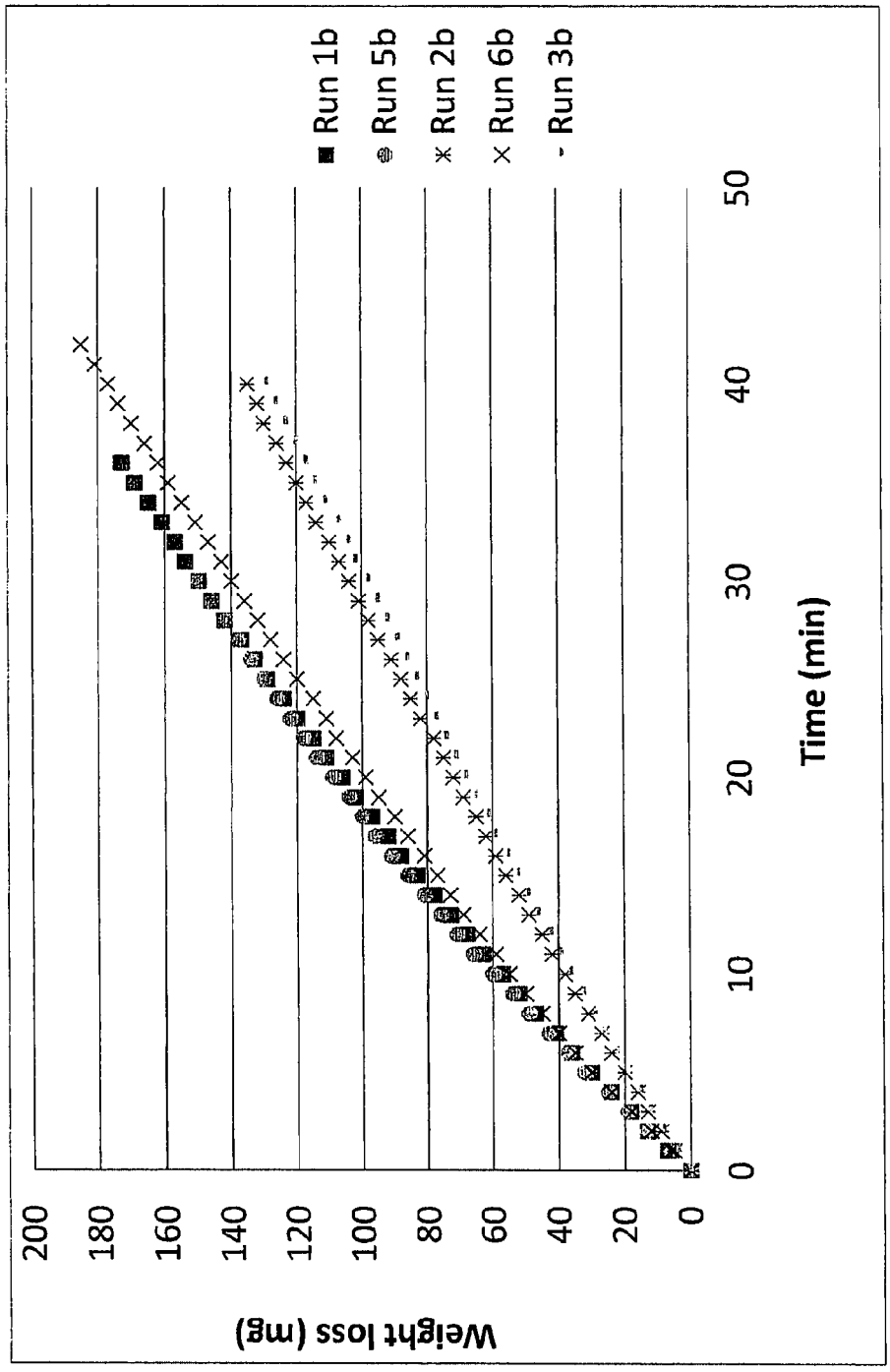

Run 1b
Run 5b
Run 2b
Run 6b
Run 3b
Weight loss (mg)
200
180
160
140
120
100
80
60
40
20
0
Time (min)
0
10
20
30
40
50

Figure 8

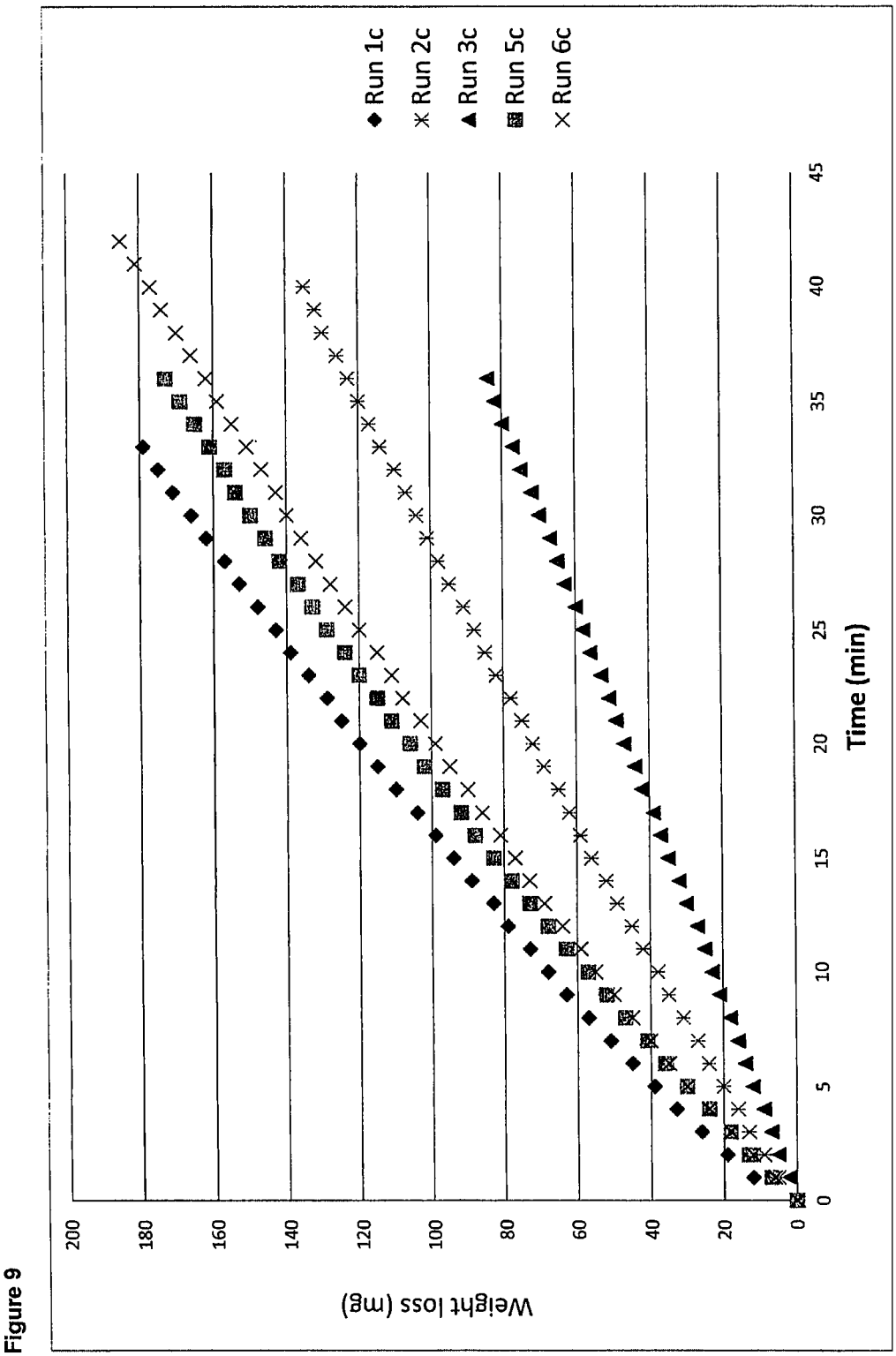

Run 1c
Run 2c
Run 3c
Run 5c
Run 6c
Weight loss (mg)
Time (min)
0
20
40
60
80
100
120
140
160
180
200
0
5
10
15
20
25
30
35
40
45

Figure 9

(TRIMETHOXYPHENYLAMINO) PYRIMIDINYL FORMULATIONS

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 13/559,805, filed Jul. 27, 2012, now issued as U.S. Pat. No. 8,771,648, which claims priority to U.S. provisional patent application No. 61/512,621 filed Jul. 28, 2011. The contents of the Ser. No. 13/559,805 application are incorporated by reference into the present application in their entirety.

FIELD OF THE INVENTION

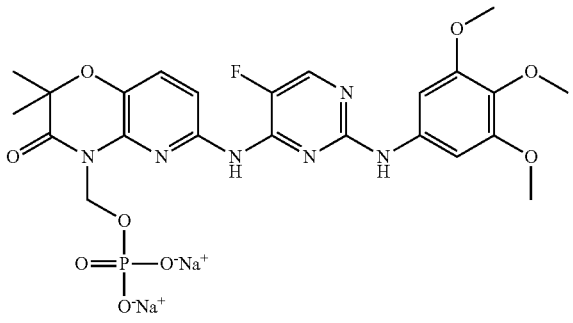
The present invention relates to pharmaceutical/formulation chemistry. The invention is understood to apply generally to formulations of compounds which contain an increased percent loading of the active ingredient. As a preferred aspect, provided herein are formulations of (6-(5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate disodium salt (Compound I) which contain an increased percent loading of Compound I. The formulations are useful for treating a variety of diseases including, but not limited to, lymphoma, immune (idiopathic) thrombocytopenia purpura (ITP), and rheumatoid arthritis (RA).

BACKGROUND OF THE INVENTION

In the manufacture of pharmaceutical formulations, it may be desirable for the drug to be administered using the smallest possible number of tablets. Thus it may be desirable for a patient to take the required dose of a drug in a single tablet rather than in more than one tablet, or in two tablets rather than in more than two tablets. Accordingly, it may be desirable for a pharmaceutical formulation to contain an increased percent loading of the active ingredient. However, it is known that increasing the percent loading of active ingredient may lead to a pharmaceutical formulation which exhibits unsatisfactory and/or variable dissolution or to a formulation which exhibits unsatisfactory and/or variable bioavailability. Such formulations may be unsuitable for use by patients.

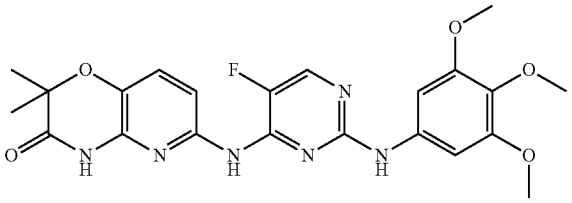
Compound I (below) is disclosed in international patent application WO2006/078846.

Compound (I)



Compound I is a pro-drug of Compound II (below). Compound II is disclosed in international patent application WO2005/016893.

Compound (II)



Hydrolytically stable pharmaceutical formulations of Compound I which include a water sequestering agent and which are prepared by a wet granulation process are disclosed in international patent application WO2009/061909.

Javaid et al (J. Pharm. Sci. 61 (9) 1972 pp 1370-1373) studied the effect of various classes of buffering agents on the dissolution of aspirin from tablet formulations.

Compound I is currently in clinical studies for the treatment of a variety of diseases such as lymphoma, ITP and RA. Dosing is currently done with orally delivered tablets with a tablet strength of 50 mg. These tablets exhibit satisfactory dissolution at low pH. However, these tablets contain a relatively low percent loading (12.5% w/w) of Compound I.

Tablets with a tablet strength of 100 mg contain an increased percent loading of Compound I. However, these tablets may exhibit unsatisfactory and/or variable dissolution at low pH. Furthermore, these tablets may exhibit unsatisfactory and/or variable bioavailability of the active ingredient.

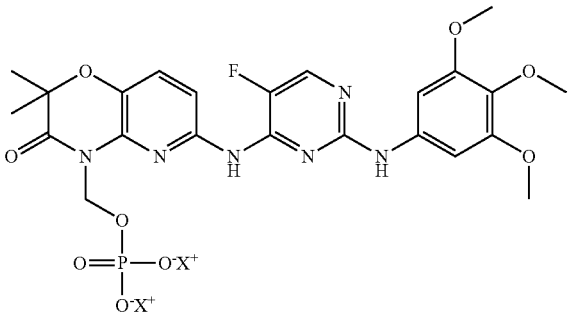
It is desirable, therefore, to produce new pharmaceutical formulations of Compound I which overcome at least in part the above problems.

DESCRIPTION OF THE INVENTION

This invention is generally directed to formulations of compounds which contain an increased percent loading of the compound of formula (I), in particular to formulations which contain an increased percent loading of active ingredient and exhibit satisfactory dissolution at low pH.

The compound of formula (I) (known hereafter as "Formula (I)") is shown below:

Formula (I)



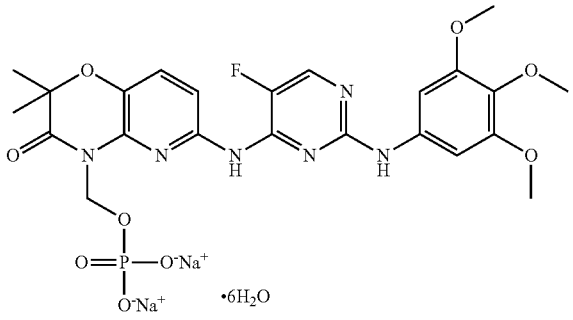
wherein each X^+ represents a monovalent cation, for example a monovalent metal cation, such as a sodium cation (Na^+), a potassium cation (K^+) or a lithium cation (Li^+);
or wherein X^+ and X^+ are taken together to represent a divalent cation X^{2+}, for example a divalent metal cation, such as a magnesium cation (Mg^{2+}), a calcium cation (Ca^{2+}) or a barium cation (Ba^{2+});

and/or hydrates thereof (such as the hexahydrate).

For example, Formula (I) may be in the form of Compound (I) above.

In another particular example, Formula (I) may be in the hexahydrate form of Compound (I) (which form is known hereafter as "Formula (II)"). The compound of Formula (II) is shown below.

Formula (II)



In particular, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and one or more effervescent agents allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and sodium hydrogen carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a yet further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and potassium hydrogen carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and magnesium carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and sodium carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and calcium carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a still further aspect, this invention provides a pharmaceutical composition comprising Formula (I) and/or hydrate thereof and potassium carbonate allowing the manufacture of tablets with an increased percent loading of Formula (I) and/or a satisfactory dissolution at low pH.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention, there is provided a pharmaceutical composition in unit dosage form comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof (for example 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg or 200 mg) and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients. For the avoidance of doubt, each of the previous integers represents a separate and independent aspect of the invention.

In another aspect of the invention a unit dosage form of the pharmaceutical composition comprises between about 60 mg to about 300 mg of Formula (I) and/or hydrate thereof.

In another aspect of the invention a unit dosage form of the pharmaceutical composition comprises between about 60 mg to about 250 mg of Formula (I) and/or hydrate thereof.

In a still further aspect, a unit dosage form of the pharmaceutical composition comprises between about 100 mg to about 200 mg of Formula (I) and/or hydrate thereof.

In a yet further aspect, a unit dosage form of the pharmaceutical composition comprises between about 125 mg to about 190 mg of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, a unit dosage form of the pharmaceutical composition comprises 63 mg±3 mg of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, a unit dosage form of the pharmaceutical composition comprises 126 mg±13 mg of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, a unit dosage form of the pharmaceutical composition comprises 190 mg±19 mg of Formula (I) and/or hydrate thereof.

In another aspect of the invention the pharmaceutical composition comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the pharmaceutical composition comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the pharmaceutical composition comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the pharmaceutical composition comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the pharmaceutical composition comprises 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the pharmaceutical composition comprises 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the pharmaceutical composition comprises less than or equal to 30% w/w of one or more effervescent agents.

In a still further aspect of the invention, the pharmaceutical composition comprises less than or equal to 25% w/w of one or more effervescent agents.

In a further aspect, the pharmaceutical composition comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the pharmaceutical composition comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the pharmaceutical composition comprises less than or equal to 10% w/w of one or more effervescent agents.

In a yet further aspect, the pharmaceutical composition comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example

between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 125 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 125 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 190 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 190 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 225 mg of Formula (I) and/or hydrate thereof and less than or equal to 150 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a unit dosage form comprising greater than or equal to 225 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further embodiment of the invention, the pharmaceutical composition and/or unit dosage form does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or hydrate thereof.

In a further aspect of the invention, optional ingredients which can be added to the pharmaceutical composition include one or more of the following:

a) fillers which, when employed, range between for example about 35 to about 75 weight percent (e.g. about 50 to about 70 weight percent) of the dry formulation;
b) binding agents which, when employed range between for example about 2 to about 8 weight percent of the dry formulation;
c) lubricants which, when employed, range from between about 0.25 and 2.0 weight percent of the dry formulation;
d) disintegrants which, when employed, range from between about 0.5 and 10.0 weight percent (e.g. about 5 weight percent) of the dry formulation; and
e) water sequestering agents, which, when employed, range from between about 2 weigh percent and 40 weight percent of the dry formulation.

In a further aspect of the invention, the pharmaceutical composition further comprises one or more additional ingredients independently selected from, for example

a) fillers such as mannitol (e.g. Pearlitol 50c, Peralitol 120c or Pearlitol 160c) or microcrystalline celluloses (e.g. MCC Avicel PH 102, Emcocel 90M, etc.);
b) binding agents such as Plasdone K29/32, Povidone, microcrystalline celluloses or Kollidon K30;
c) lubricants such as magnesium stearate;
d) disintegrants such as sodium starch glycolate, for example ExploTab or Glycolys LV;
e) Water sequestering agents such as starch (e.g. sodium starch glycolate), magnesium sulfate, calcium chloride, silica, kaolin, microcrystalline celluloses etc.

In another aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention, there is provided a tablet comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof (for example 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg or 200 mg) and an amount of one or more effervescent agents (that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients. For the avoidance of doubt, each of the previous integers represents a separate and independent aspect of the invention.

In another aspect of the invention, the tablet comprises between about 60 mg to about 300 mg of Formula (I) and/or hydrate thereof.

In another aspect of the invention the tablet comprises between about 60 mg to about 250 mg of Formula (I) and/or hydrate thereof.

In a still further aspect, the tablet comprises between about 100 mg to about 200 mg of Formula (I) and/or hydrate thereof.

In a yet further aspect, the tablet comprises between about 125 mg to about 190 mg of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the tablet comprises 63 mg±3 mg of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the tablet comprises 126 mg±13 mg of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the tablet comprises 190 mg±19 mg of Formula (I) and/or hydrate thereof.

In another aspect of the invention the tablet comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the tablet comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the tablet comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the tablet comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the tablet comprises 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the tablet comprises 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the tablet comprises less than or equal to 30% w/w of one or more effervescent agents.0

In a further aspect, the tablet comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the tablet comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the tablet comprises less than or equal to 10% w/w of one or more effervescent agents.

In a further aspect of the invention, the tablet comprises less than or equal to 75 mg of one or more effervescent agents.

In a yet further aspect, the tablet comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a tablet comprising greater than or equal to 60 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further aspect of the invention, there is provided a tablet comprising greater than or equal to 125 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further aspect of the invention, there is provided a tablet comprising greater than or equal to 125 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a tablet comprising greater than or equal to 190 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a tablet comprising greater than or equal to 190 mg of Formula (I) and/or hydrate thereof and less than or equal to 75 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a tablet comprising greater than or equal to 225 mg of Formula (I) and/or hydrate thereof and less than or equal to 150 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a yet further aspect of the invention, there is provided a tablet comprising greater than or equal to 225 mg of Formula (I) and/or hydrate thereof and less than or equal to 110 mg of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further embodiment of the invention, the tablet does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or a hydrate thereof.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral administration.

These dosage forms will usually include one or more pharmaceutically acceptable excipients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings or colorants. It will be understood that an individual excipient may be multifunctional. Examples of pharmaceutically acceptable excipients are described in the Handbook of Pharmaceutical Excipients (Fifth Edition, 2005, edited by Ray C. Rowe, Paul J. Sheskey and Sian C. Owen, published by the American Pharmaceutical Association and the Pharmaceutical Press). The active ingredients of the present invention may be administered by oral or parenteral (e.g. intravenous, subcutaneous, intramuscular or intraarticular) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. The active ingredients may also be delivered to the lung and/or airways via oral administration in the form of a solution, suspension, aerosol or dry powder formulation. As will be

understood by those skilled in the art, the most appropriate method of administering the active ingredients is dependent on a number of factors.

It will be understood that the therapeutic dose of each active ingredient administered in accordance with the present invention will vary depending upon the particular active ingredient employed, the mode by which the active ingredient is to be administered, and the condition or disorder to be treated.

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

In a further aspect of the invention, optional ingredients which can be added to the compositions disclosed herein include one or more of the following:

a) fillers which, when employed, range between for example about 35 to about 75 weight percent (e.g. about 50 to about 70 weight percent) of the dry formulation;

b) binding agents which, when employed range between for example about 2 to about 8 weight percent of the dry formulation;

c) lubricants which, when employed, range from between about 0.25 and 2.0 weight percent of the dry formulation;

d) disintegrants which, when employed, range from between about 0.5 and 10.0 weight percent (e.g. about 5 weight percent) of the dry formulation; and

a) water sequestering agents, which, when employed, range from between about 2 weigh percent and 40 weight percent of the dry formulation;

In a further aspect of the invention, the tablet further comprises one or more additional ingredients independently selected from, for example:

a) fillers such as mannitol (e.g. Pearlitol 50c, Peralitol 120c or Pearlitol 160c) or microcrystalline celluloses (e.g. MCC Avicel PH 102, Emcocel 90M, etc.);

b) binding agents such as Plasdone K29/32, Povidone, microcrystalline celluloses or Kollidon K30;

c) lubricants such as magnesium stearate;

d) disintegrants such as sodium starch glycolate, for example ExploTab or Glycolys LV;

a) Water sequestering agents such as starch (e.g. sodium starch glycolate), calcium chloride, silica, kaolin, microcrystalline celluloses etc.

In a further aspect of the invention, the pharmaceutical composition or unit dosage form comprises the compound of Formula (I) and/or hydrate thereof, one or more effervescent agents and a filler (such as mannitol). In a further aspect of the invention, the pharmaceutical composition or unit dosage form comprises the compound of Formula (I) and/or hydrate thereof, one or more effervescent agents, a filler (such as mannitol) and a binding agent (such as Povidone). In a further aspect of the invention, the pharmaceutical composition or unit dosage form comprises the compound of Formula (I) and/or hydrate thereof, one or more effervescent agents, a filler (such as mannitol), a binding agent (such as Povidone) and a disintegrant (such as sodium starch glycolate). In another aspect the pharmaceutical composition or unit dosage form comprises the compound of Formula (II), one or more effervescent agents, a filler (such as mannitol), a binding agent (such as Povidone), a disintegrant (such as sodium starch glycolate) and a lubricant (such as magnesium stearate).

In a yet further aspect of the invention, the pharmaceutical composition comprises the following components by weight:

Composition 1 (mg)		Composition 2 (mg)		Composition 3 (mg)	
Formula (II)	126	Formula (II)	190	Formula (II)	63
Mannitol	249	Mannitol	185	Mannitol	62
Sodium hydrogen carbonate	75	Sodium hydrogen carbonate	75	Sodium hydrogen carbonate	25
Sodium starch glycolate	25	Sodium starch glycolate	25	Sodium starch glycolate	8
Povidone	15	Povidone	15	Povidone	5
Magnesium stearate	10	Magnesium stearate	10	Magnesium stearate	3

In a yet further aspect of the invention, the pharmaceutical composition comprises the following components (% w/w):

Composition 1 (% w/w)		Composition 2 and 3 (% w/w)	
Formula (II)	25	Formula (II)	38
Mannitol	50	Mannitol	37
Sodium hydrogen carbonate	15	Sodium hydrogen carbonate	15
Sodium starch glycolate	5	Sodium starch glycolate	5
Povidone	3	Povidone	3
Magnesium stearate	2	Magnesium stearate	2

In a still further aspect, the invention comprises a tablet formed from the pressing of Composition 1 and/or Composition 2 into tablet form. In a still further aspect, the invention comprises a tablet formed from the pressing of Composition 3 into tablet form.

In a separate aspect of the invention, there is provided a process for the preparation of a pharmaceutical composition, as hereinbefore defined, which process comprises bringing into association Formula (I) and/or hydrate thereof with a pharmaceutically acceptable adjuvant, diluents or carrier.

In a further aspect of the invention, there is provided a process for the preparation of a pharmaceutical composition which process comprises mixing Formula (I) and/or hydrate thereof with one or more effervescent agents optionally in the presence of one or more pharmaceutically acceptable ingredients (Step A). In a further aspect, Step A is carried out in the presence of one or more fillers (such as mannitol) and optionally in the presence of one or more pharmaceutically acceptable ingredients. In a still further aspect, Step A is carried out in the presence of one or more fillers (such as mannitol) and optionally in the presence of one or more binding agents and/or one or more disintegrants.

In a further aspect of the invention, there is provided a further process for the preparation of a pharmaceutical composition as defined above which process comprises adding purified water and/or binder solution into the powder mixture from Step A above and mixing to form enlarged granules and optionally passing through a filter screen to break-up large agglomerates (Step B). In a further aspect between about 10% and 45% by weight of purified water is added into the powder mixture.

In a further aspect of the invention, there is provided a further process for the preparation of a pharmaceutical composition which process comprises drying the enlarged granules produced in Step B above until an LOD of less than 10% (e.g. less than 5%) is achieved, to provide dried granules (Step C).

In a further aspect of the invention there is provided a process for the preparation of a pharmaceutical composition which process (wet granulation process) comprises:

a) blending Formula (I) and/or hydrate thereof with one or more effervescent agents, one or more fillers (such as mannitol) and optionally in the presence of one or more binding agents and/or one or more disintegrants and/or one or more other excipients;

b) adding between about 10% and 45% by weight of purified water and/or binder solution into the powder mixture of a) above and mixing to form enlarged granules and optionally passing through a filter screen to break-up large agglomerates; and

c) drying the enlarged granules produced in b) above until an LOD of less than 10% (e.g. less than 5%) is achieved, to provide dried granules.

The dried granules prepared in the methods above are typically between about 25 μm to about 2000 μm in diameter.

In another of its method aspects, this invention further comprises milling the dried granules. In one aspect, the dried granules are milled so that about 90 weight percent have a particle size between about 25 μm to about 2000 μm in diameter.

In yet another aspect, the dried, milled, granules are mixed with a lubricant until homogenous, and then the resulting pharmaceutical composition is tabletted. Suitable lubricants include stearic acid (e.g. magnesium stearate), colloidal silica and talc.

In an alternative aspect of the invention, the lubricant (such as magnesium stearate) can be added to the dry granules prior to milling, and then the resulting pharmaceutical composition is milled and then tabletted.

In another aspect, this invention provides a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of an effervescent that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the wet granulation formulation comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the wet granulation formulation comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the wet granulation formulation comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the wet granulation formulation comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the wet granulation formulation contains 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the wet granulation formulation contains 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the wet granulation formulation comprises less than or equal to 30% w/w of one or more effervescent agents.

In a further aspect, the wet granulation formulation comprises less than or equal to 25% w/w of one or more effervescent agents.

In a further aspect, the wet granulation formulation comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the wet granulation formulation comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the wet granulation formulation comprises less than or equal to 10% w/w of one or more effervescent agents.

In a yet further aspect, the wet granulation formulation comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a wet granulation formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the wet granulation formulation comprises Formula (I) and/or hydrate thereof, water, one or more effervescent agents, filler(s), binding agent(s) and disintegrant(s).

In a still further embodiment of the invention, the wet granulation formulation does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or a hydrate thereof.

In another aspect, this invention provides a tablet formed by compressing the wet granulation formulation.

In a further aspect of the invention, there is provided a further process for the preparation of a pharmaceutical composition as defined above which process comprises passing the mixture of Step A above through a compactor to produce dry granules (Step D).

In a further aspect of the present invention there is provided a process for the manufacture of a pharmaceutical composition which process (roller compaction process) comprises:

(a) blending Formula (I) and/or hydrate thereof with one or more effervescent agents, one or more fillers (such as mannitol) and optionally in the presence of one or more binding agents and/or one or more disintegrants and/or one or more other excipients;

(b) passing the mixture of (a) above through a compactor to produce dry granules.

The dried granules prepared in the methods above are typically between about 25 μm to about 2000 μm in diameter.

In another of its method aspects, this invention further comprises milling the dried granules. In one aspect, the dried granules are milled so that about 90 weight percent have a particle size between about 25 μm to about 2000 μm in diameter.

In another aspect, a lubricant is added to the mixture of (a) above prior to passing through a compactor. Suitable lubricants include stearic acid (e.g. magnesium stearate), colloidal silica and talc.

In yet another aspect, the resulting pharmaceutical composition is tabletted. In an alternative aspect of the invention, the lubricant (such as magnesium stearate) can be added to the dry granules prior to milling, and then the resulting pharmaceutical composition is milled and then tabletted.

In another aspect, this invention provides a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the roller compaction formulation comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the roller compaction formulation comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the roller compaction formulation comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the roller compaction formulation comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the roller compaction formulation contains 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the roller compaction formulation contains 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the roller compaction formulation comprises less than or equal to 30% w/w of one or more effervescent agents.

In a further aspect, the roller compaction formulation comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the roller compaction formulation comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the roller compaction formulation comprises less than or equal to 10% w/w of one or more effervescent agents.

In a yet further aspect, the roller compaction formulation comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a roller compaction formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of an effervescent; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the roller compaction formulation comprises Formula (I) and/or hydrate thereof, one or more effervescent agents, filler(s), binding agent(s), lubricant(s) and disintegrant(s).

In a still further embodiment of the invention, the roller compaction formulation does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or a hydrate thereof.

In another aspect, this invention provides a tablet formed by compressing the roller compaction formulation.

In a further aspect of the invention there is provided a process for the manufacture of a pharmaceutical composition which process (direct compression process) comprises:

(a) blending Formula (I) and/or hydrate thereof with one or more effervescent agents, one or more fillers (such as mannitol) and optionally in the presence of one or more binding agents and/or one or more disintegrants and/or one or more lubricants and/or one or more other excipients;

(b) compressing the mixture of (a) above.

In another aspect of the invention the direct compression formulation comprises Formula (I) and/or hydrate thereof, one or more effervescent agents, filler(s), binding agent(s), lubricant(s) and disintegrant(s).

In another aspect, this invention provides a tablet formed directly by compressing the mixture of (a) above.

In another aspect, this invention provides a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and an amount of one or more effervescent agents that is sufficient to provide satisfactory in vitro dissolution; and further comprising one or more pharmaceutically acceptable ingredients.

In another aspect of the invention the direct compression formulation comprises between about 15% w/w to about 60% w/w of Formula (I) and/or hydrate thereof.

In a further aspect, the direct compression formulation comprises between about 20% w/w to about 50% w/w of Formula (I) and/or hydrate thereof.

In a still further aspect, the direct compression formulation comprises between about 25% w/w to about 40% w/w of Formula (I) and/or hydrate thereof.

In another aspect of the invention the direct compression formulation comprises greater than or equal to 25% w/w of Formula (I) and/or hydrate thereof.

In a specific aspect of the invention, the direct compression formulation contains 25%±2.5% w/w of Formula (I) and/or hydrate thereof.

In a further specific aspect of the invention, the direct compression formulation contains 38%±3.8% of Formula (I) and/or hydrate thereof.

In a still further aspect of the invention, the direct compression formulation comprises less than or equal to 30% w/w of one or more effervescent agents.

In a further aspect, the direct compression formulation comprises less than or equal to 20% w/w of one or more effervescent agents.

In a still further aspect, the direct compression formulation comprises less than or equal to 15% w/w of one or more effervescent agents.

In a still further aspect, the direct compression formulation comprises less than or equal to 10% w/w of one or more effervescent agents.

In a yet further aspect, the direct compression formulation comprises greater than or equal to about 5% w/w of one or more effervescent agents, for example between about 5% to 50%, for example between about 5% to 40%, for example between about 5% to 30%, for example between about 5% to 25%, for example between about 5% to 20%, for example between about 5% to 15%, for example between about 5% to 10%. For the avoidance of doubt, each of the previous examples represents a separate and independent aspect of the invention.

In a further aspect of the invention, there is provided a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 25% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 20% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 15% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a further aspect of the invention, there is provided a direct compression formulation comprising greater than 15% w/w of Formula (I) and/or hydrate thereof and less than or equal to 10% w/w of one or more effervescent agents; and further comprising one or more pharmaceutically acceptable ingredients.

In a still further embodiment of the invention, the direct compression formulation does not comprise an acidifying ingredient (for example does not comprise citric acid). For the avoidance of doubt the term "acidifying ingredient" does not include the compound of Formula (I) or the free acid thereof or a hydrate thereof.

The pharmaceutical composition and/or tablet and/or wet granulation formulation and/or roller compaction formulation and/or direct compression formulation can additionally and optionally include a colourant, as long as it is approved and certified by the FDA. For example, exemplary colours include allura red, acid fuschin D, napthalone red B, food orange 8, eosin Y, phloxine B, erythrosine, natural red 4, carmine, red iron oxide, yellow iron oxide, black iron oxide, titanium dioxide and the like.

Sweetening agents can also be added to the pharmaceutical composition and/or tablet and/or wet granulation formulation and/or roller compaction formulation and/or direct compression formulation or to the outer core of the tablet to create or add to the sweetness. Saccharide fillers and binders, e.g. mannitol, lactose, and the like, can add to this effect. For example, cyclamates, saccharin, aspartame, acesulfame K (Mukherjee (1997) Food Chem. Toxicol. 35:1177-1179), or the like (Rolls (1991) Am. J. Clin. Nutr. 53:872-878), can be used. Sweeteners other than sugars have the advantage of reducing the bulk volume of the pharmaceutical composition and/or tablet (core tablet and/or coat) and/or wet granulation formulation and/or roller compaction formulation and/or direct compression formulation and not affecting the physical properties of the tablet.

It will be understood by the skilled person that the incorporation of one or more effervescent agents into the pharmaceutical composition may necessitate the use of appropriate packaging. In a further aspect of the invention, there is provided packaging suitable for a pharmaceutical composition wherein the pharmaceutical composition comprises one or more effervescent agents. Examples of such packaging include packaging providing moisture protection. Examples of such packaging include for example PVC packaging, PVC/PVDC packaging, PVC/CTFE packaging, OPA/aluminium/PVC packaging, aluminium packaging or aluminium blister packaging. Further examples of such packaging include bottles with or without desiccants.

Compounds of the invention can be used to treat or prevent autoimmune diseases and/or symptoms of such diseases and are expected to be useful as a therapeutic and prophylactic agent for diseases associated with an abnormal immune response (e.g. autoimmune diseases and allergic diseases) and various infections and cancers which are required for activation of an immune response. For example, compounds of the invention may be administered to a mammal, including man, for the treatment of the following non-limiting examples of autoimmune conditions or diseases: rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome. Compounds of the invention may be administered to a mammal, including man, for the treatment of the following non-limiting examples of cancers: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumours and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes.

According to a further feature of the present invention there is provided a method for treating an autoimmune disease state in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) and/or a hydrate thereof.

The invention also provides a compound of Formula (I) and/or a hydrate thereof, for use in therapy.

In another aspect the invention provides the use of a compound of Formula (I) and/or a hydrate thereof in the manufacture of a medicament for use in therapy.

In a further aspect, there is provided a method for treating rheumatoid arthritis in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) and/or a hydrate thereof.

The invention also provides a compound of Formula (I) and/or a hydrate thereof, for use in the treatment of rheumatoid arthritis.

In another aspect the invention provides the use of a compound of Formula (I) and/or a hydrate thereof in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

In a further aspect, there is provided a method for treating systemic lupus erythematosus in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) and/or a hydrate thereof.

The invention also provides a compound of Formula (I) and/or a hydrate thereof, for use in the treatment of systemic lupus erythematosus.

In another aspect the invention provides the use of a compound of Formula (I) and/or a hydrate thereof in the manufacture of a medicament for use in the treatment of systemic lupus erythematosus.

In a further aspect, there is provided a method for treating cancer in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) and/or a hydrate thereof.

The invention also provides a compound of Formula (I) and/or a hydrate thereof, for use in the treatment of cancer.

In another aspect the invention provides the use of a compound of Formula (I) and/or a hydrate thereof in the manufacture of a medicament for use in the treatment of cancer.

DEFINITIONS

As used herein, the term "effervescent agent" refers to any pharmaceutically acceptable material which evolves a gas when placed in an aqueous environment, for example the evolution of carbon dioxide on acidification. An example of an effervescent agent is a carbonate, for example a metal carbonate (such as sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate or aluminium carbonate) or an organic carbonate (such as disodium glycine carbonate, dimethyl carbonate or ethylene carbonate). A further example of an effervescent agent is a bicarbonate, for example a metal bicarbonate (such as sodium hydrogen carbonate or potassium hydrogen carbonate). For the avoidance of doubt, each of the effervescent agents referred to above represents a separate and independent aspect of the invention.

In one particular aspect of the invention, the effervescent agent is selected from a carbonate or bicarbonate. In another particular aspect of the invention, the effervescent agent is selected from a metal carbonate or a metal bicarbonate. In another particular aspect of the invention, the effervescent agent is selected from sodium hydrogen carbonate, potassium hydrogen carbonate, magnesium carbonate or sodium carbonate. In a further particular aspect of the invention, the effervescent agent is sodium hydrogen carbonate.

For the avoidance of doubt, reference to either a % w/w or to a weight (in mgs) of "one or more effervescent agents" in any aspect of the invention refers to the combined total % w/w or the combined total weight (in mgs) of all effervescent agents. By way of example, a pharmaceutical composition comprising 10% w/w of sodium hydrogen carbonate and 10% w/w magnesium carbonate would comprise 20% w/w of "one or more effervescent agents".

As used herein, the term "binding agent" refers to a pharmaceutically acceptable compound or composition added to a formulation to hold the active pharmaceutical ingredient and inactive ingredients together in a cohesive mix. Dry binders used for direct compaction must exhibit cohesive and adhesive forces so that when compacted the particles agglomerate. Binders used for wet granulation are hydrophilic and soluble in water and are usually dissolved in water to form a wet mass that is then granulated. Examples of suitable binding agents includes, but are not limited to, Povidone, Plasdone K29/32, Plasdone S-630, hydropropyl cellulose, methylcellulose, polyvinylpyrrolidone, aluminium stearate, hydroxypropylmethylcellulose and the like. It is possible for such binding agents to additionally act as water sequestering agents (e.g. Povidone).

As used herein, the term "filler" refers to any pharmaceutically acceptable material or composition added to a formulation to add bulk. Suitable fillers include, but are not limited to, mannitol, lactose, microcrystalline cellulose, silified microcrystalline cellulose and dicalcium phosphate.

As used herein, the term "lubricant" refers to any pharmaceutically acceptable agent which reduces surface friction, lubricates the surface of the granule, decreases tendency to build-up of static electricity, and/or reduces friability of the granules. Thus, lubricants can serve as anti-agglomeration agents. Examples of suitable lubricants are magnesium stearate, stearic acid, sodium stearyl fumarate, colloidal silica, talc, other hydrogenated vegetable oil or triglycerides.

As used herein, the term "disintegrant" refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Examples of disintegrants include, but are not limited to, non-saccharide water soluble polymers, such as cross-linked povidine. Other disintegrants that can also be used include, e.g. croscarmellose sodium, sodium starch glycolate, and the like, e.g. see Khattab (1992) J. Pharm. Pharmacol. 45:687-691.

The term "drying" and "dried" refer to a process which decreases the water content of a composition to a desired level.

The terms "compressing", "molding" and "pressing" refer to the process of applying compressive force to a formulation (powder or granules), as within a die, to form a tablet. The terms "compressed tablet" and "pressed tablet" mean any tablet formed by such a process.

The term "tablet" is used in its common context, and refers to a solid composition made by compressing and/or molding a mixture of compositions in a form convenient for swallowing or application to any body cavity.

As used herein, "tablet strength" is the equivalent mass of the free acid form of Compound I based on the amount of Formula (II) present in the tablet. Thus by way of example, a tablet strength of 50 mg will contain about 63 mg of Formula (II).

As used herein, "percent loading" is calculated by reference to the amount of Formula (II).

The term "low pH" refers to a measured pH of less than 5, such as less than 3, for example between 0 and 3.

The term "satisfactory in vitro dissolution" refers to a percent dissolution of greater than or equal to 70% within 30 minutes in 0.1N hydrochloric acid solution at 37° C.±0.5° C. as measured using the general procedure of the United States Pharmacopeia (Apparatus 2).

Dissolution Performance of the Existing Tablet

Reference Table 1 shows the composition of the tablet of Formula (II) with a tablet strength of 50 mg (the 50 mg tablet) as currently administered in ongoing clinical trials together with an equivalent tablet of Formula (II) with a tablet strength of 100 mg (the 100 mg tablet). The tablets were prepared in accordance with WO2009/061909.

Tablet strength is the equivalent mass of the free acid form of Compound I based on the amount of Formula (II) present in the tablet. Thus by way of example, a tablet strength of 50 mg will contain about 63 mg of Formula (II). The percent loading of Formula (II) in the 50 mg tablet is 12.5% whereas the percent loading of Formula (II) in the 100 mg tablet is 25%.

REFERENCE TABLE 1

Material	50 mg tablet (% w/w)	100 mg tablet (% w/w)
Formula (II)	12.5	25.0
Pregelatinised starch	37.02	30.77
Sodium starch glycolate	5.77	5.77
Microcrystalline cellulose	37.02	30.77
Povidone	2.88	2.88
Magnesium stearate	0.96	0.96
Opadry II Blue 85F99003	3.85	3.85

Dissolution was determined according to the general procedure of the United States Pharmacopeia using Apparatus 2 with 900 mL of 0.1N hydrochloric acid solution at 37° C.±0.5° C. and stirrer speed of 75 rpm. At 5, 15, 30, 45 and 60 minutes, 10 mL of dissolution solution was withdrawn and filtered through a 0.45 μM PTFE filter. The concentration of Formula (II) in solution was determined by uv spectroscopy (e.g. Agilent 8453) at a wavelength of 324 nm and path length of 2 mm against an external standard solution.

Table 2 shows the resulting tablet percent dissolution in 0.1N hydrochloric acid for the 50 mg reference tablet and for three separate batches of the 100 mg tablet having the reference formulation set forth in Table 1 after 30 minutes. A plot showing the dissolution profile over time is shown in FIG. **1**.

TABLE 2

Formulation Strength (mg)	Formula (II) (% w/w)	Mean % dissolution in 0.1N HCl at 30 minutes
50	12.5	87
100 - A	25	65
100 - B	25	41
100 - C	25	16

The 100 mg tablet exhibits unsatisfactory and/or variable dissolution performance (varying between 16% and 65%). This compares to the 50 mg tablet which exhibits satisfactory dissolution.

We have investigated a number of formulations where the percent loading of Formula (II) is 25% or greater, in a desire to increase the mean percent dissolution performance of a tablet which contains an increased percent loading of Formula (II). Mannitol, microcrystalline cellulose, silified microcrystalline cellulose, sodium chloride and di-sodium hydrogen phosphate, and individual combinations thereof, all failed to provide a percent dissolution in 0.1N hydrochloric acid after 30 minutes of greater than 50%. In addition, formulations which comprised citric acid, arginine, meglumine and Polyplasdone Crospovidine or combinations thereof also failed to provide satisfactory dissolution.

It was therefore surprising to find that formulations which contained an effervescent agent exhibited satisfactory dissolution, even where said formulations contained an increased percent loading of Formula (II) (e.g. 25% and/or 37.5%, and up to 50%).

Table 3 shows the selection of components for sixteen separate experiments to investigate dissolution in a tablet with an increased percent loading of Formula (II). The results are shown in FIG. **2**. Table 4 shows the selection of components for a further eight experiments and the results for these are shown in FIG. **3**. Tables 10 and 11 (in Example 6) show the selection of components for a further twelve experiments and the results for these are shown in FIG. **6**. In each case, all experiments which did not use an effervescent agent failed to achieve a percent dissolution in 0.1N hydrochloric acid after 30 minutes of greater than 50%. However, experiments which used an effervescent agent showed satisfactory dissolution. For the avoidance of doubt, the reference to water in Tables 3 and 4 refers to the amount of water added during the processing of the formulation and prior to any subsequent drying step. The composition of any final tablet form will not include the level of water indicated.

TABLE 3

Run	Formula (II) (% w/w)	Filler 1	Filler 2	Disintegrant (5% w/w)	SLS (% w/w)	MgSt (% w/w)	Water (% w/w)
1	25.0	Mannitol	Sodium Bicarbonate	SSG	0	1	15
2	25.0	Mannitol	MCC	CCS	0	1	35
3	37.5	SMCC	Sodium Bicarbonate	SSG	0	1	25
4	37.5	Mannitol	Sodium Bicarbonate	SSG	5	1	15
5	37.5	SMCC	MCC	CCS	0	1	55
6	37.5	SMCC	MCC	SSG	5	1	55
7	25.0	SMCC	MCC	CCS	5	1	55

TABLE 3-continued

Run	Formula (II) (% w/w)	Filler 1	Filler 2	Disintegrant (5% w/w)	SLS (% w/w)	MgSt (% w/w)	Water (% w/w)
8	25.0	Mannitol	MCC	SSG	5	1	35
9	25.0	SMCC	Sodium Bicarbonate	CCS	0	1	40
10	37.5	Mannitol	Sodium Bicarbonate	CCS	0	1	25
11	25.0	SMCC	MCC	SSG	0	1	55
12	37.5	Mannitol	MCC	SSG	0	1	30
13	37.5	SMCC	Sodium Bicarbonate	CCS	5	1	30
14	25.0	SMCC	Sodium Bicarbonate	SSG	5	1	30
15	37.5	Mannitol	MCC	CCS	5	1	35
16	25.0	Mannitol	Sodium Bicarbonate	CCS	5	1	15

TABLE 4

Run	Cmpd I (% w/w)	MCC (% w/w)	Filler 1	Filler 1 (% w/w)	PVP (% w/w)	SSG (% w/w)	MgSt (% w/w)	Mannitol (% w/w)	Water (% w/w)
1	37.9	15	disodium hydrogen phosphate	30	3	5	1.5	7.1	22.5
2	37.9	0	disodium hydrogen phosphate	10	3	5	1.5	42.1	20
3	37.9	0	sodium hydrogen carbonate	30	3	5	1.5	22.1	15
4	25.2	0	disodium hydrogen phosphate	10	3	5	1.5	54.8	17.5
5	25.2	0	disodium hydrogen phosphate	30	3	5	1.5	34.8	25
6	25.2	15	disodium hydrogen phosphate	10	3	5	1.5	39.8	25
7	25.2	15	sodium hydrogen carbonate	30	3	5	1.5	19.8	18.3
8	37.9	15	sodium hydrogen carbonate	10	3	5	1.5	27.1	26.7

Whilst we do not wish to be limited by theoretical considerations, the addition of an effervescent agent (such as sodium hydrogen carbonate) appears to change the disintegration mechanism from a swelling disintegration mechanism, wherein high drug loading prevents rapid hydration/swelling events and consequently leads to slower disintegrating tablets which only dissolves slowly, to an erosion dissolution mechanism. In particular, it is thought that incorporation of an effervescent agent (such as sodium hydrogen carbonate) allows the tablet to rapidly disintegrate (break) into small particles which dissolve quickly.

Manufacturing Process

The particular manufacturing process of this invention for wet granulation formulations comprises premixing all of the required formulation components except water and lubricant(s). In one preferred aspect, premixing is conducted in a mixer-granulator such as a PMA25, and premixing comprises mixing the components together at impeller speeds ranging between about 50 to about 500 rpm for a period of between about 2 to about 20 minutes. In another preferred aspect, batches were dry-blended for 4 minutes at 440 rpm with a chopper speed of 1500 rpm using a Diosna granulator P1/6.

Water is then sprayed onto/into the dry composition to form a wet granulation formulation described herein. The water is added at for example a constant rate over a period of for example from about 0.05 kg/min to about 1.0 kg/min with either constant mixing during addition or mixing after addition. In either event, mixing is continued until the wet granulation composition is homogenous. In an alternative aspect, water is added at a rate of 15 mL/min to a total volume of 8-12% (w/w).

The wet granulation formulation is then dried using conventional techniques to reduce water to a predetermined level. In one aspect, the water content of the dried granulated formulation is less than about 10% (for example about 5%) by weight. Drying can be conducted at various temperatures and times. One skilled in the art could readily determine the appropriate drying times based on the initial water content, the desired final water content, and the drying temperature(s) employed.

The particular manufacturing process of this invention for roller compaction formulations comprises preblending all of the required formulation components until homogenous. In one preferred aspect, preblending is conducted in a blender-

granulator such as a Copley Mobile Blender, and preblending comprises mixing the components together at speeds ranging between about 50 to about 500 rpm for a period of between about 2 to about 20 minutes.

The homogenous mix is then passed through a roller compactor, such as an Alexanderwerk WP120 to produce dry granules.

The dried granulated formulation produced via the wet granulation and/or roller compaction process is milled using conventional techniques and machinery. In one aspect, the formulation is milled through an appropriate mesh screen using commercially available milling equipment such as, e.g. Quadro Comil.

Following milling, the lubricant(s) (for example magnesium stearate) is added to the granulated formulation which is then blended using conventional techniques and machinery. Alternatively, the lubricant(s) (such as magnesium stearate) can be added to the dry granules prior to milling.

The pressing or compressing of the dried, granulated, milled and blended formulation can be accomplished using any tablet press. Many alternative means to effect this step are available, and the invention is not limited by the use of any particular equipment. In one aspect, the compression step is carried out using a Piccola Riva PV tablet press. In another aspect, the compression step is carried out by using an F3 Manesty press.

The diameter and shape of the tablet depends upon the die and punches selected for the compression of the milled and mixed formulation. Tablets can be discoid, oval, oblong, round, cylindrical, triangular, and the like. The tablets may be scored to facilitate breaking. The top or lower surface can be embossed or debossed with symbols or letters.

The compression force can be selected based on the type/model of press, a desired hardness of the resulting tabets, as well as other attributes such as friability, disintegration or dissolution characteristics, etc.

The particular manufacturing process of this invention for direct compression formulations comprises preblending all of the required formulation components. In one preferred aspect, all of the required formulation components except lubricants) are mixed in a mixer-granulator (such as a PMA25 at impeller speeds ranging between about 50 to about 500 rpm for a period of between about 2 to about 20 minutes), and thereafter lubricants) added and the resulting mixture blended (using for example a WAB turbula at speeds ranging between about 50 to about 500 rpm for a period of between about 2 to about 20 minutes). The resulting mixture is then compressed into tablet core using conventional techniques.

DESCRIPTION OF FIGURES

FIG. **1** shows a plot of the percent dissolution in 0.1N hydrochloric acid of existing tablets of strength 50 mg and 100 mg versus time.

FIG. **2** shows a plot of the percent dissolution in 0.1N hydrochloric acid of sixteen alternative tablet forms versus time.

FIG. **3** shows a plot of the percent dissolution in 0.1N hydrochloric acid of a further eight alternative tablet forms versus time.

FIG. **4** shows a plot of the percent dissolution in 0.1N hydrochloric acid of eight tablet forms obtained via a roller compaction process versus time.

FIG. **5** shows a plot of the percent dissolution in 0.1N hydrochloric acid of a tablet form obtained via a direct compression process versus time.

FIG. **6** shows a plot of the percent dissolution in 0.1N hydrochloric acid of a further twelve alternative tablet forms versus time.

FIG. **7** shows a plot of weight loss versus time of five tablet forms after placing the tablets in 0.1 N HCl (run 1).

FIG. **8** shows a plot of weight loss versus time of five tablet forms after placing the tablets in 0.1 N HCl (run 2).

FIG. **9** shows a plot of weight loss versus time of five tablet forms after placing the tablets in 0.1 N HCl (run 3).

EXAMPLES

The invention is further understood by reference to the following examples, which are intended to be purely exemplary of the invention. The present invention is not limited in scope by the exemplified aspects, which are intended as illustrations of single aspects of the invention only. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications fall within the scope of the appended claims.

In the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

GMP=good manufacturing practice
LOD=loss on drying
mg=milligram
MgSt=magnesium stearate
min=minute
mL=milliliter
nm=nanometer
JP=Japanese Pharmacopeia 15th Edition, English Version (Society of Japanese Pharmacopoeia) 2006
PhEur=European Pharmacopoeia 6th Edition (Directorate for the Quality of Medicines of the Council of Europe) 2009
PTFE=polytetrafluoroethylene
PVP=polyvinylpyrrolidone
rpm=revolutions per minute
SLS=sodium lauryl sulphate
SSG=sodium starch glycolate
USP-NF=United States Pharmacopeia 31/National Formulary 26 (The United States Pharmacopeia Convention) 2008
uv=ultraviolet
w/w=weight for weight

Table 5 below shows materials used, pharmacopeial status, grade and supplier.

TABLE 5

Material	Pharmacopeia	Grade	Supplier
Mannitol	PhEur USP-NF JP	Pearlitol 160c Pearlitol 120c Parteck M200	Roquette Freres S.A. (France)
Cellulose, microcrystalline	PhEur USP-NF JP	Avicel ® PH-101 Avicel ® PH-102	FMC Biopolymer (Ireland)
Sodium chloride	Ph Eur BP JP USP	Emprove	Merck Chemicals Ltd (UK)
di-Sodium hydrogen phosphate	Ph Eur BP USP	Emprove	Merck Chemicals Ltd (UK)

TABLE 5-continued

Material	Pharmacopeia	Grade	Supplier
Sodium hydrogen carbonate	Ph Eur BP JP USP	Emprove	Merck Chemicals Ltd (UK)
Sodium starch glycolate	Ph Eur USP-NF	Glycolys LV	Roquette Freres S.A. (France)
Croscarmellose sodium	Ph Eur USP JP	Ac-di-Sol	FMC Biopolymer (Ireland)
Magnesium stearate	Ph Eur USP-NF JP	NF Non Bovine	Mallinckrodt (USA)
Povidone	Ph Eur USP	Kollidon 30 K29/32	BASF (Germany) ISP (Germany)
Sodium lauryl sulphate (Sodium dodecyl sulfate)	USP NF	N/A	Sigma Aldrich (UK)
Silified microcrystalline cellulose	Ph Eur JP NF	Prosolv 50	JRS Pharma (Germany)
Pre-gelatinised starch 1500	Ph Eur NF	Starch 1500	Colorcon (USA)
Colloidal silica	USP-NF	Aeorsil	Evonik (Germany)

Table 6 below shows equipment used, model and supplier.

TABLE 6

Make	Model	Supplier
Diosna	P1/6	Dierks & Söhne Gmbh, Osnabrück, Germany
Quadro	Comil U3 & Comil 194	Quadro Engineering, Waterloo, Canada
WAB	Turbula T2F	Willy A. Bachofen AG, Muttenz, Switzerland
Riva	Piccola Nova	RivaSA, Buenos Aires, Argentina
Aeromatic	Strea 1	Casburt Pharmaceutical Equipment, Stoke-on-Trent, UK
Alexanderwerk	WP 120	Alexanderwerk AG, Remscheid, Germany
Copley Mobile Blender	Mobile Blender	Copley Scientific, Nottingham, UK
Niro-Fielder	PMA25	Aeromatic Fielder, Eastleigh, UK
Fette	1200	Fette Compacting GmbH, Schwarzenbek, Germany
Aeromatic-Fielder	MP1	Aeromatic Fielder, Eastleigh, UK
Vector	MFL.01	Vector Corporation, Marion, IA, U.S.A
F3	Manesty	Manesty, Knowsley, UK

Example 1

Assessment of Dissolution Performance of Sixteen Alternative Tablet Forms

Sixteen different prototype tablets were prepared from a wet granulation formulation using methods well known to those skilled in the art. The composition of each of these tablets is set out in Table 3 above (not including water).

Formula (II) and the excipients described in Table 3 (total batch size approximately 250 g) are charged to a mixer-granulator (Diosna, 1 L) and mixed for 5 minutes at 300 rpm. Purified water (ranging from 15% w/w to 55% w/w as set out in Table 3) is added to the powders with further mixing until a suitable wet mass is formed (ranging from 7 to 17 mins) at 300 rpm. The resultant granules are dried to appropriate moisture content (≤6% LOD) using a fluid bed dryer (Vector) with an inlet air temperature of 60° C. The dried granules are milled using an appropriately sized screen (1 mm, Quadro Comil U3). Magnesium stearate is then added to the granules, which are then blended (WAB turbula) for 5 mins at 55 rpm before compressing into tablet cores using conventional tabletting equipment (F3 tablet press).

Dissolution was determined in accordance with the procedure outlined in the description above and the dissolution profiles are shown in FIG. **2**.

Example 2

Assessment of Dissolution Performance of a Further Eight Alternative Tablet Forms

A further eight different prototype tablets were prepared from a wet granulation formulation using methods well known to those skilled in the art. The composition of each of these tablets is set out in Table 4 above (not including water).

Formula (II) and the excipients described in Table 4 (total batch size approximately 600 g) are charged to a mixer-granulator (Diosna, 4 L) and mixed. Purified water (ranging from 15% w/w to 26.7% w/w as set out in Table 4) is added to the powders with further mixing until a suitable wet mass is formed (ranging from 10 to 24 mins) at 200 rpm. The resultant granules are dried to appropriate moisture content (≤5% LOD) using a fluid bed dryer (Aeromatic Strea) with an inlet air temperature of 100° C. The dried granules are milled using an appropriately sized screen (1 mm, Quadro Comil U3). Magnesium stearate is then added to the granules, which are then blended (WAB turbula) for 10 mins at 50 rpm before compressing into tablet cores using conventional tabletting equipment (Riva Piccola).

Dissolution was determined in accordance with the procedure outlined in the description above and the dissolution profiles are shown in FIG. **3**.

Example 3

Assessment of Dissolution Performance of Tablets of Formula (II) Prepared by Roller Compaction Process

Eight formulations selected from Examples 2 and 3 were assessed for feasibility in a roller compaction process using methods well known to those skilled in the art. The composition of each of these formulations is set out in Table 7 below.

Formula (II) and the excipients described in Table 7 (total batch size approximately 1.5 kg) are charged to a mixer to produce a homogenous mix (Copley Mobile Blender) for 5 minutes at 30 rpm. The homogeneous mix is then passed through a roller compactor (Alexanderwerk, 40 mm roller size, 25 bar roller pressure, 2.5 rpm roller speed, 2.0 mm roller-gap size) to produce dry granules. The dry granules are then blended with magnesium stearate (Copley Mobile Blender). The resultant granules are compressed into tablet cores using conventional tabletting equipment (Riva Piccola).

TABLE 7

	Formulation (% w/w)							
Component	1	2	3	4	5	6	7	8
Formula (II)	37.9	25.2	37.9	37.9	37.9	37.9	37.9	37.9
Mannitol	22.1	54.8	27.1	27.1	45.1	45.1	42.1	45.1
(Silicified) Micro-crystalline cellulose	0	0	15	15	10	10	10	10

TABLE 7-continued

Component	Formulation (% w/w) 1	2	3	4	5	6	7	8
Sodium hydrogen carbonate	30	10	10	10	0	0	0	0
Povidone	3	3	3	3	0	0	3	0
Sodium Starch glycolate	5	5	5	5	5	5	5	5
Colloidal silica	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Intragranular Magnesuim Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Extragranular Magnesuim Stearate	1	1	1	1	1	1	1	1

Formulations 1, 2, 3 and 8 were manufactured using Pearlitol 160C. The remaining formulations used Parteck M200 mannitol. Formulations 3, 4, 6 and 7 used microcrystalline cellulose (Avicel PH101). Formulations 5 and 8 used silicified microcrystalline cellulose (Prosolv 50).

Dissolution was determined in accordance with the procedure outlined in the description above and the dissolution profiles are shown in FIG. **4**.

Example 4

Assessment of Dissolution Performance of Tablets of Formula (II) Prepared by Direct Compression

Tablets were prepared using direct compression formulation using methods well known to those skilled in the art. The composition of the tablets is as per Table 3, Run 9 above (without the addition of water).

Formula (II) and the excipients described in Table 3, Run 9 (total batch size approximately 250 g) are charged to a mixer-granulator (Diosna, 1 L) and mixed for 5 minutes at 300 rpm. Magnesium stearate is then added to the blend, which is then blended (WAB Turbula) for 5 minutes at 55 rpm before compressing into tablet cores using conventional tabletting equipment (F3 tablet press).

Dissolution was determined in accordance with the procedure outlined in the description above and the dissolution profiles are shown in FIG. **5**.

Example 5

Preparation of Tablets of Formula (II)

Tablets containing the components set out in Table 8 below were prepared using methods well known to those skilled in the art, in particular using conventional mixing, wet granulation, compression and film coating processes, according to GMP.

Formula (II), mannitol, sodium hydrogen carbonate, sodium starch glycolate and povidone are charged to a mixer-granulator (PMA25) and mixed. Purified water is added to the powders with further mixing until a suitable wet mass is formed. The wet mass may be passed through a screen to break up any large agglomerates. The resultant granules are dried to appropriate moisture content (≤5% LOD) using a fluid bed dryer (MP1). The dried granules are milled using an appropriately sized screen (for example 1.1 mm, Comil 194). Magnesium stearate is then added to the granules, which are then blended (Copley) before compressing into tablet cores using conventional tabletting equipment (Fette 1200).

TABLE 8

Tablet strength Components	50 mg mg/ tablet	100 mg mg/ tablet	150 mg mg/ tablet	Standard
Formula (II)	63.1	126.2	189.3	AstraZeneca
Mannitol	61.8	248.6	185.3	Ph Eur, NF, JP
Sodium hydrogen carbonate	25.0	75.0	74.9	Ph Eur, USP, JP
Sodium starch glycolate	8.3	25.0	25.0	Ph Eur, NF
Povidone	5.0	15.0	15.0	Ph Eur, USP, JP, NF
Magnesium stearate	3.3	10.0	10.0	Ph Eur, NF

Example 6

Assessment of Dissolution Performance of Additional Tablet Forms

Potassium hydrogen carbonate ($KHCO_3$), magnesium carbonate ($MgCO_3$) and sodium carbonate (Na_2CO_3) were incorporated into the tablet formulation in place of sodium hydrogen carbonate. The level of each was corrected to evolve the same quantity of carbon dioxide.

Sodium carbonate (Na_2CO_3) was incorporated at two concentrations to provide better understanding of the mechanism of action of these effervescent agents in the formulation. This took advantage of the fact that the reaction of sodium carbonate with hydrochloric acid takes place in two stages:

Stage I: sodium carbonate is converted to sodium hydrogen carbonate ($NaHCO_3$) as shown in the reaction:

$$Na_2CO_3+HCl \rightarrow NaHCO_3+NaCl$$

Stage II: the gas, carbon dioxide is released

$$NaHCO_3+HCl \rightarrow NaCl+H_2O+CO_2$$

Accordingly, sodium carbonate has stronger alkalizing activity compared to sodium hydrogen carbonate due to its capability to accept two hydrogen ions but has slower effervescent activity as evolution of the gas (CO_2) requires two steps reaction to take place.

Therefore, two levels of sodium carbonate were investigated. The lower level (9.5%) gave similar alkalisation capacity to 15% sodium hydrogen carbonate but with a lower amount of CO_2 to evolve in acidic environment. The higher level (15%) evolved the same total amount of CO_2 as 15% sodium hydrogen carbonate but at slower rate and with higher alkalisation capacity.

In addition, arginine and meglumine were investigated as alternatives to sodium hydrogen carbonate. Arginine and meglumine provide alkalising activity without any effervescent activity.

Moreover, citric acid was incorporated in one formulation to provide acidity to the microenvironment of the tablets and counteract the alkalising effect of sodium hydrogen carbonate. The level of citric acid was adjusted to neutralise the alkalinity of sodium hydrogen carbonate.

Furthermore, incorporation of higher levels of Formula (II) in the formulation was included at two levels of sodium hydrogen carbonate, 15% and 25%, to address possible cor-

relation between the quantities of Formula (II) and the quantity of sodium hydrogen carbonate required to allow satisfactory dissolution.

Additonally, Polyplasdone® Crospovidone superdisintegrant was investigated in the formulation to replace sodium hydrogen carbonate and sodium starch glycolate in order to provide the possibility for rapid disintegration through a combination of swelling and wicking mechanism of disintegrations. Polyplasdone disintegrants are highly compressible materials and therefore higher level could be used to provide quicker disintegration. Polyplasdone® Crospovidone was investigated at two concentration 10% and 15%. Meglumine was included in these two formulations to provide high local pH (to prevent active pharmaceutical ingredient (API) gelling in acidic environment) and consequently offering a better opportunity to achieve complete dissolution in acid.

The formulation components and composition for each of the alternative tablet forms in Example 6 are presented in Tables 9, 10 and 11.

TABLE 9

Component	Supplier/Trade name	Function
Formula (II)	AstraZeneca/DSM Linz	Active Pharmaceutical Ingredient
Mannitol	Roquette Pearlitol 50C	Filler
sodium hydrogen carbonate (NaHCO3)	Merck Emprove	effervescent/ alkalizing agent
Potassium hydrogen carbonate (KHCO3)	Merck EMPROVE ® exp Ph Eur, BP, USP, FCC, E 501	effervescent/ alkalizing agent
magnesium carbonate (MgCO3)	Merck Emprove, Heavy	effervescent/ alkalizing agent
sodium carbonate (Na2CO3)	Merck EMPROVE ® exp Ph Eur, BP, NF, anhydrous	effervescent/ alkalizing agent
Citric Acid	Merck EMPROVE ® exp Ph Eur, BP, JP, USP, E 330, FCC, anhydrous	Acidifying agent
L-arginine (Arg)	Merck EMPROVE ® exp Ph Eur, USP	alkalizing agent
Meglumine (Megl)	Merck EMPROVE ® api Ph Eur, JP, USP	alkalizing agent
Crospovidone (CrosPosv)	Polyplasdone ® Crospovidone	Disintegrant
Sodium Starch Glycolate (SSG)	Expltab	Disintegrant
Polyvinylpyrrolidone (PVP)	BASF Kollidon K30	Binder
Magnesium Stearate (MgSt)	Mallinkrodt non-bovine	Lubricant

Batches of drug substance and excipients were dispensed to form a total nominal batch size of 600 g (Table 11). Magnesium stearate was included in the nominal total but was not included during granulation. Following drying, magnesium stearate was added to make up 2% of the total dry granules.

A wet granulation process was used to prepare the granules for tabletting using the method below.

Batches were dry blended for 4 min at 440 rpm with chopper speed of 1500 rpm using Diosna granulator P1/6 (Dierks & Söhne Gmbh, Osnabrück, Germany) in the 4 L bowl.

Water was added drop wise at a rate of 15 mL min-1 to a total volume of 8-12% (w/w). The endpoint was checked by passing a sample of powder through a 1 mm sieve and judging whether there were fines and whether most of the materials were granular.

The wet mass was dried using Niro-Aeromatic Strea fluid bed dryer (Casburt Pharmaceutical Equipment, Stoke-on-Trent, UK) with a maximum inlet temperature of 90° C. and an appropriate fluidizing airflow. Extent of drying was determined using a moisture analyser (Mettler Toledo HB43) to <2%.

The dried granular mass was milled at 3000 rpm through a 1.0 mm screen using a U3 bench top Quadro Comil mill (Quadro Engineering, Waterloo, Canada).

The lubricant was then added at level of 2% by weight of the dried mass of granules and was blended using a Turbula blender (Willy A. Bachofen AG, Muttenz, Switzerland) at 50 rpm for 15 min.

The resultant mixtures were compressed using an F3 Manesty press (Casburt Pharmaceutical Equipment, Stoke-on-Trent, UK). The target compression force was 14 kN as used during A23 [RITA.000-376-136]. The compression force was assessed using DAAS instrumentation (Waltti Electronics Ltd., Kuopio, Finland).

Batches were compressed using 11 mm round concave tooling. Tablets were compressed to a target weight of 500 mg. Some tablets were collected from the line to allow weight and hardness to be correlated with compression force.

The resultant tablets were de-dusted and kept in air tight plastic bottles for analysis.

TABLE 10

	Run											
	1	2	3	4	5	6	7	8	9	10	11a	11b
Formula (II) (%)	37.9	37.9	37.9	37.9	37.9	37.9	37.9	37.9	37.9	37.9	50	50
NaHCO3 (%)	15	0	0	15	0	0	0	0	0	0	15	25
Na2CO3 (%)	0	15	9.465	0	0	0	0	0	0	0	0	0
Citric acid (%)	0	0	0	34.305	0	0	0	0	0	0	0	0
KHCO3 (%)	0	0	0	0	17.88	0	0	0	0	0	0	0
MgCO3 (%)	0	0	0	0	0	15.06	0	0	0	0	0	0
Arg (%)	0	0	0	0	0	0	31.1	0	0	0	0	0
Megl (%)	0	0	0	0	0	0	0	34.86	34.86	34.86	0	0
CrosPove (%)	0	0	0	0	0	0	0	0	10	15	0	0
SSG (%)	5	5	5	5	5	5	5	5	0	0	5	5
PVP (%)	3	3	3	3	3	3	3	3	33	3	33	3
MgSt (%)	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol (%)	37.1	37.1	42.64	2.795	34.22	37.04	20.99	17.24	12.24	7.24	25	15

TABLE 11

	1	2	3	4	5	6	7	8	9	10	11a	11b
Formula (II) (g)	227.4	227.4	227.4	227.4	227.4	227.4	227.4	227.4	227.4	227.4	300	300
NaHCO3 (g)	90	0	0	90	0	0	0	0	0	0	90	150
Na2CO3 (g)	0	90	56.79	0	0	0	0	0	0	0	0	0
Citric acid (g)	0	0	0	205.83	0	0	0	0	0	0	0	0
KHCO3 (g)	0	0	0	0	107.28	0	0	0	0	0	0	0
MgCO3 (g)	0	0	0	0	0	90.36	0	0	0	0	0	0
Arg (g)	0	0	0	0	0	0	186.66	0	0	0	0	0
Megl (g)	0	0	0	0	0	0	0	209.16	209.16	209.16	0	0
CrosPove (g)	0	0	0	0	0	0	0	0	60	90	0	0
SSG (g)	30	30	30	30	30	30	30	30	0	0	30	30
PVP (g)	18	18	18	18	18	18	18	18	18	18	18	18
MgSt (g)	12	12	12	12	12	12	12	12	12	12	12	12
Mannitol (g)	222.6	222.6	255.8	16.77	205.3	222.2	125.9	103.4	73.44	43.44	150	90

Disintegration time was measured using an Erweka Copley ZT74 disintegration machine. The experiment was carried out at 36-38° C. using 0.7 L tap water and the disc method. Six tablets were tested for each batch. Results are presented as mean±SD (n=6).

Sotax HT100 was used to determine the weight, hardness, thickness and diameter of 15 tablets from each batch. The Sotax is an automated tablet tester, which measures each parameter at a different station for a specified number of tablets using a specific method ("11 mm 500 mg Round Uncoated n15"). First the weight is measured, then the tablet is passed to a thickness gauge before being passed to a jaw where the diameter and hardness are measured. A report is then generated with individual data for each of the tablets tested, as well as the calculated mean and RSD for each batch. Results are presented as mean±SD (n=15).

The true density of the tablets was obtained by helium pycnometry using the AccuPyc. Ten tablets were weighed accurately, placed in the sample cup previously used for calibration and analysed. True density was calculated for each batch using the equation set out below and was found to be between 1.55 and 1.56 g/cc for each of them.

$$\text{True density} = (\text{mass/volume of solids})$$

Tablet envelope density (apparent density) was then obtained by a volume displacement method using the GeoPyc. The same ten tablets were then placed in the 25.4 cm cylinder with DryFlo. The porosity was calculated by the GeoPyc using the true density data from above and the following equation:

$$\text{Apparent density} = (\text{mass of tablets/envelope volume of tablets})$$

The porosity of the tablets was then determined using the apparent density and true density calculated above in the following equation:

$$\text{Porosity} = 100 \times 1 - (\text{apparent density/true density})$$

Dissolution was determined in accordance with the procedure outlined in the description above.

The amount of gas evolved as a result of the tablets being placed in an acidic environment was assessed. A 250 ml beaker filled with 100 ml of 0.1 N HCl (pH 1) was placed over a balance connected to a PC to transmit the weight at regular time interval (every 15 seconds). The balance was left to settle until the balance reading was stable. One tablet was dropped in the beaker and weight recording was started. The weight difference was calculated and plotted as a function of time.

Weight, hardness, disintegration time and porosity data are summarised in Table 12.

TABLE 12

	Weight (mg)		Hardness (kp)		Disintegration time (s)		Porosity (%)	
	Average	SD	Average	SD	Average	SD	Average	SD
1	500.3	5.00	9	0.9	327.5	25.03	13.10	0.39
2	501.6	10.43	9	2.4	475.5	43.72	15.43	0.37
3	476.3	15.86	7	2.7	426.16	39.42	13.90	0.23
5	505.4	3.08	9	0.7	454	23.41	12.66	0.33
6	487.2	13.03	10	2	134	9.01	15.99	0.06
7	493	19.53	8	2.7	338	10.12	14.62	0.29
8	491.1	26.68	11	3.1	360.0	26.50	10.33	0.10
9	509.2	6.17	15	1.7	367.0	97.6	9.18	0.14
10	499.1	7.72	9	1.1	516.7	15.2	14.66	0.14
11a	504.4	12.29	9	2.2	461.3	19.2	14.19	0.05
11b	499.4	16.9	9	2	487.2	56.4	12.66	0.17

The dissolution profiles of the tablets in 0.1 M HCl are presented in FIG. **6**. No result is given for Run 4 as no satisfactory formulation could be achieved and therefore no dissolution measurement was taken.

Results from gas evolution quantification are presented in FIGS. **7**, **8** and **9**.

The results showed that alkalising agents which did not additionally provide effervescent activity failed to provide tablets of Formula (II) which gave satisfactory dissolution. The results suggest that effervescent agents such as sodium hydrogen carbonate, potassium hydrogen carbonate and magnesium carbonate enhance the dissolution of the tablet.

The tablet with a lower level of sodium carbonate provided a lower level of dissolution compared to the tablet with a higher level of sodium carbonate. Furthermore, the tablet with the higher level of sodium carbonate provided dissolution at a lower rate and extent compared to tablets with sodium hydrogen carbonate. This could be explained as a result of slower carbon dioxide evolution.

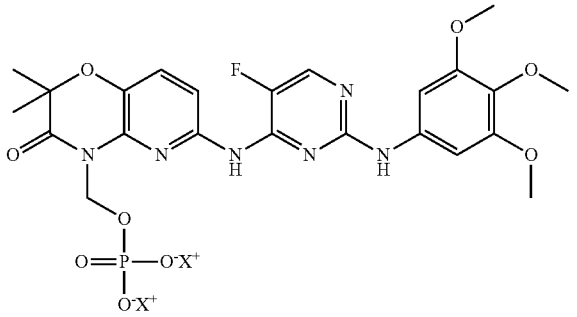
Accordingly, the rate and extent of carbon dioxide evolution appear to effect the dissolution profile of the tablet.

The results further show that increased drug loading (for example greater than or equal to 50% w/w of Formula (II)) exhibiting a satisfactory dissolution profile can be achieved using sodium hydrogen carbonate. Furthermore, the results show that higher levels of sodium hydrogen carbonate (greater than or equal to 25%) were not necessary to achieve a satisfactory dissolution profile.

The invention claimed is:

1. A method of treating a patient for rheumatoid arthritis, which method comprises administering to said patient a pharmaceutical composition comprising greater than 15% w/w of the compound of Formula (I):

Formula (I)



and/or a hydrate thereof;

wherein each X^+ represents a monovalent cation; and

an amount of one or more effervescent agents sufficient to provide satisfactory in vitro dissolution of said compound at low pH; and

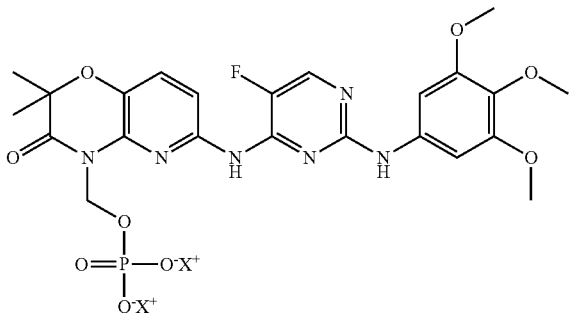
further comprising one or more pharmaceutically acceptable ingredients.

2. The method according to claim **1** wherein each X^+ in the compound of Formula (I) represents a sodium cation (Na^+).

3. The method according to claim **1** wherein the compound of Formula (I) is in the form of a hexahydrate.

4. A method of treating a patient for cancer, which method comprises administering to said patient a pharmaceutical composition comprising greater than 15% w/w of the compound of Formula (I):

Formula (I)



and/or a hydrate thereof;

wherein each X^+ represents a monovalent cation; and

an amount of one or more effervescent agents sufficient to provide satisfactory in vitro dissolution of said compound at low pH; and

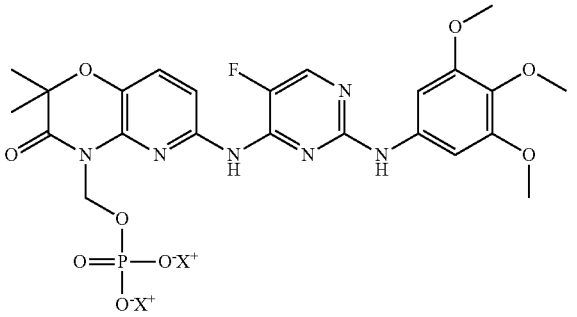
further comprising one or more pharmaceutically acceptable ingredients.

5. The method according to claim **4** wherein each X^+ in the compound of Formula (I) represents a sodium cation (Na^+).

6. The method according to claim **4** wherein the compound of Formula (I) is in the form of a hexahydrate.

7. A method of treating a patient for systemic lupus erythematosus, which method comprises administering to said patient a pharmaceutical composition comprising greater than 15% w/w of the compound of Formula (I):

Formula (I)



and/or a hydrate thereof;

wherein each X^+ represents a monovalent cation; and

an amount of one or more effervescent agents sufficient to provide satisfactory in vitro dissolution of said compound at low pH; and

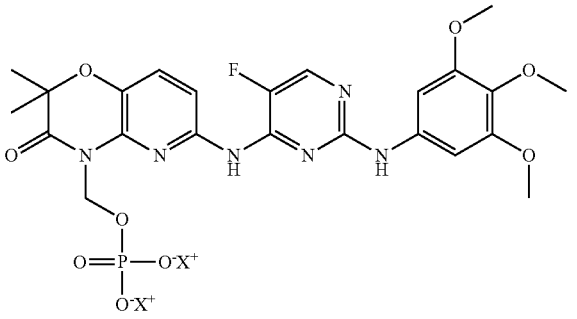
further comprising one or more pharmaceutically acceptable ingredients.

8. The method according to claim **7** wherein each X^+ in the compound of Formula (I) represents a sodium cation (Na^+).

9. The method according to claim **7** wherein the compound of Formula (I) is in the form of a hexahydrate.

10. A method of treating a patient for rheumatoid arthritis, which method comprises administering to said patient unit dosage form comprising greater than or equal to 60 mg of the compound of Formula (I):

Formula (I)



and/or a hydrate thereof;

wherein each X^+ represents a monovalent cation; and

less than or equal to 110 mg of one or more effervescent agents sufficient to provide satisfactory in vitro dissolution of said compound at low pH; and

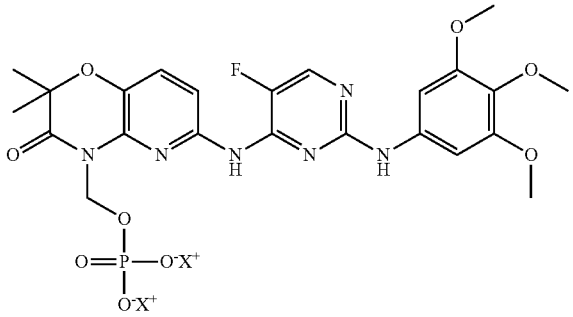
further comprising one or more pharmaceutically acceptable ingredients.

11. The method according to claim **10** wherein each X^+ in the compound of Formula (II) represents a sodium cation (Na^+).

12. The method according to claim **10** wherein the compound of Formula (II) is in the form of a hexahydrate.

13. A method of treating a patient for cancer, which method comprises administering to said patient unit dosage form comprising greater than or equal to 60 mg of the compound of Formula (I):

Formula (I)



and/or a hydrate thereof;

wherein each X^+ represents a monovalent cation; and

less than or equal to 110 mg of one or more effervescent agents sufficient to provide satisfactory in vitro dissolution of said compound at low pH; and

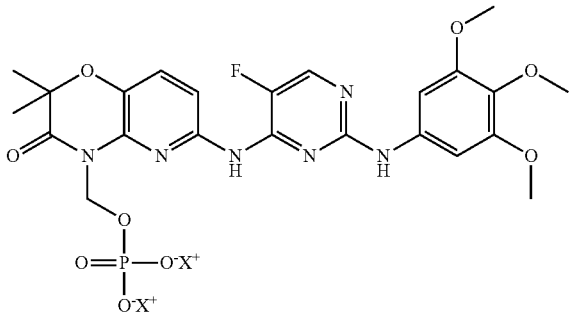
further comprising one or more pharmaceutically acceptable ingredients.

14. The method according to claim **13** wherein each X^+ in the compound of Formula (II) represents a sodium cation (Na^+).

15. The method according to claim **13** wherein the compound of Formula (II) is in the form of a hexahydrate.

16. A method of treating a patient for systemic lupus erythematosus, which method comprises administering to said patient unit dosage form comprising greater than or equal to 60 mg of the compound of Formula (I):

Formula (I)



and/or a hydrate thereof;

wherein each X^+ represents a monovalent cation; and

less than or equal to 110 mg of one or more effervescent agents sufficient to provide satisfactory in vitro dissolution of said compound at low pH; and

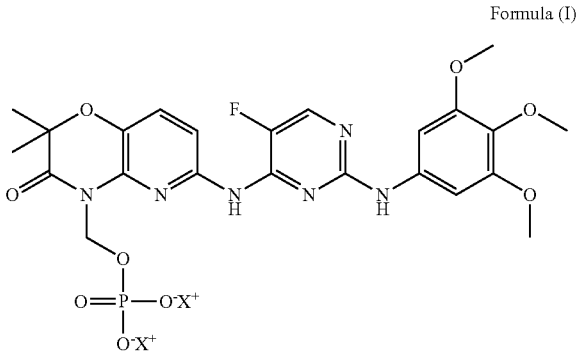
further comprising one or more pharmaceutically acceptable ingredients.

17. The method according to claim **16** wherein each X^+ in the compound of Formula (II) represents a sodium cation (Na^+).

18. The method according to claim **16** wherein the compound of Formula (II) is in the form of a hexahydrate.

19. A method of treating a patient for immune thrombocytic purpura, which method comprises administering to said patient a pharmaceutical composition comprising greater than 15% w/w of the compound of Formula (I):

Formula (I)



and/or a hydrate thereof;

wherein each X^+ represents a monovalent cation; and

an amount of one or more effervescent agents sufficient to provide satisfactory in vitro dissolution of said compound at low pH; and

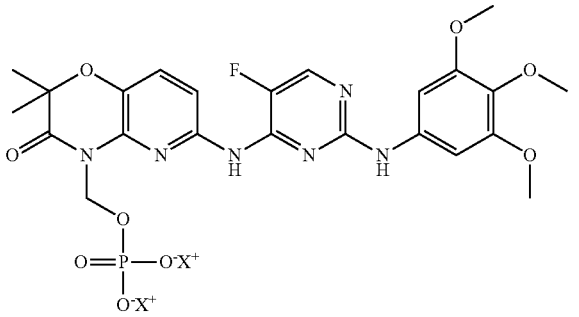
further comprising one or more pharmaceutically acceptable ingredients.

20. The method according to claim **19** wherein each X^+ in the compound of Formula (I) represents a sodium cation (Na^+).

21. The method according to claim **19** wherein the compound of Formula (I) is in the form of a hexahydrate.

22. A method of treating a patient for immune thrombocytic purpura, which method comprises administering to said patient unit dosage form comprising greater than or equal to 60 mg of the compound of Formula (I):

Formula (I)



and/or a hydrate thereof;

wherein each X^+ represents a monovalent cation; and

less than or equal to 110 mg of one or more effervescent agents sufficient to provide satisfactory in vitro dissolution of said compound at low pH; and

further comprising one or more pharmaceutically acceptable ingredients.

23. The method according to claim **22** wherein each X^+ in the compound of Formula (II) represents a sodium cation (Na^+).

24. The method according to claim **22** wherein the compound of Formula (II) is in the form of a hexahydrate.

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